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A retrospective study of the relationship between methotrexate clearance and hyperuricemia following high-dose methotrexate therapy

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Recent studies have revealed that methotrexate (MTX) is excreted by organic anion transporters (OATs), which can be inhibited by uric acid (UA). It has been reported that renal clearance of MTX was decreased in hyperuricemic rats. Here we report the relationship between MTX clearance and hyperuricemia in high-dose MTX (HDMTX) chemotherapy. The authors retrospectively studied the concentration of UA in serum and the MTX clearance of 10 patients (21 cases) with HDMTX from Kagoshima University Hospital (Kagoshima, Japan). The serum UA concentration of 21 cases was significantly increased after HDMTX (pre-HDMTX: 4.11 ± 1.36 mg/dl, post-HDMTX: 5.78 ± 1.77 mg/dl, mean ± SD, p<0.0005). Abnormal values of UA (greater than 7 mg/dl) were observed in 6 cases in this study. The serum concentration of UA was transiently increased. A positive correlation between the elevation rate of serum UA and the half-life of MTX (r=0.618; p=0.002; 95%CI, 0.254 to 0.829) was observed. In conclusion, this retrospective study shows that HDMTX treatment induces hyperuricemia, suggesting that hyperuricemia may be a risk factor for delayed clearance of MTX in HDMTX chemotherapy.

**Keywords:** Hyperuricemia, Methotrexate, Therapeutic drug monitoring, Uric acid
INTRODUCTION

Methotrexate (MTX) is an antifolate compound widely used in anticancer chemotherapy. High-dose MTX (HDMTX) treatment with leucovorin (LV) rescue has been used as a therapeutic strategy in oncology for more than 20 years (Ackland and Schilsky, 1987). HDMTX chemotherapy is well established as a treatment for childhood acute lymphocytic leukemia and osteosarcoma (Treon and Chabner, 1996).

It is known that the serum concentration of MTX correlates to the toxicity of MTX. Therapeutic drug monitoring (TDM) of MTX plays a crucial role in safe and effective HDMTX chemotherapy. It has been reported that the onset toxicity of MTX was 10 µM at 24 hours, 1 µM at 48 hours and 0.1 µM at 72 hours following MTX treatment (Sasaki and Fujimoto, 1979). Delayed MTX elimination relates to the toxicity of MTX (Relling et al., 1994).

Recent studies have revealed that MTX is excreted by drug transporters, which are kidney-specific organic anion transporters, organic anion transporters (OATs) and multidrug resistance proteins (MRPs) (Borst et al., 2000; Van Aubel et al., 2000). OATs and MRPs play important roles in the elimination of a variety of endogenous substances, xenobiotics and their metabolites from the body (Sekine et al., 2000; Gerk and Vore, 2002). An endogenous substance, uric acid, inhibits the transport of MTX via OAT1 and OAT3 in vitro (Sekine et al., 1997; Cha et al., 2001). In this study, we retrospectively determined the relationship between the concentration of serum MTX and serum biochemical parameters following HDMTX chemotherapy.

SUBJECTS AND METHODS

The authors analyzed the results of therapeutic drug monitoring (TDM) of MTX and biochemical parameters of HDMTX-treated patients for eight years from April 1998 to March 2006 at Kagoshima University (Kagoshima, Japan). TDM of MTX was performed in 473 cases over eight years. Among 473 cases, 21 cases were analyzed in this study. Eligibility criteria for this retrospective study included the following: i) The values of serum MTX concentration at 24 hours and 48 hours were applied for the values of direct observation; ii) TDM was performed at least three times after HDMTX. The half-life (t1/2) and MRT (mean residence time) of MTX was calculated by moment analysis. Statistics analyses were performed using paired Student’s t test. The correlations were evaluated by Fisher’s r to z test.

RESULTS

The patient characteristics are shown in Table 1. Three patients had malignant lymphoma while 18 cases had osteosarcoma. Table 2 shows the biochemical parameters of pre- and post-HDMTX. HDMTX significantly increased the serum concentration of UA. Abnormal values of UA (greater

| Table 1. Patient characteristics and pharmacokinetics parameters of MTX |
|--------------------------|----------|--------------------------|
| Number of patients       | 10       | Number of cases           | 21       |
| Number of cases          | 21       | Male                      | 5        |
| Female                   | 5        | Age                       | 14.8 ± 10.2 |
| Dose (mg/kg)             | 304.4 ± 115.9 |
| MTX concentration 24-hour (µM) | 67.5 ± 156.9 |
| MTX concentration 48-hour (µM) | 15.1 ± 54.5 |
| MRT (h)                  | 10.6 ± 6.3 |
| t1/2 (h)                 | 14.2 ± 9.8 |

Note: Date represent the means ± SD. The values of serum MTX concentration at 24 hours and 48 hours were applied for direct observation value.

| Table 2. Alternation of the biochemical parameters in patients with HDMTX chemotherapy |
|------------------------------------------|----------|--------------------------|
| n                                        | Pre-HDMTX | Post-HDMTX |
| Uric acid (mg/dl)                        | 21        | 4.11±1.36               |
| 4.11±1.36                                | 5.78±1.77*** |
| AST (IU/dl)                              | 21        | 21.6±9.3                |
| 21.6±9.3                                 | 715.8±944.8** |
| ALT (IU/dl)                              | 21        | 27.4±22.4               |
| 27.4±22.4                                | 767.3±907.9** |
| Total protein (mg/dl)                    | 12        | 6.93±0.57               |
| 6.93±0.57                                | 6.48±0.50* |
| Total bilirubin (mg/dl)                  | 19        | 0.47±0.27               |
| 0.47±0.27                                | 1.47±0.63*** |
| Creatinine (mg/dl)                       | 21        | 0.48±0.14               |
| 0.48±0.14                                | 0.67±0.28* |

Note: ALT: alanine aminotransferase, AST: aspartate aminotransferase. Data represent the means ± SD. *: p<0.05, **: p<0.005, ***: p<0.0005, compared with pre-HDMTX
than 7 mg/dl) were observed in six cases. HDMTX also increased serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, total bilirubin and creatinine (Cr) as presented in Table 2. These biochemical parameters were transiently increased and then returned to the basal level.

There was good correlation between the elevation rate of the serum concentration of UA and the half-life ($t_{1/2}$) of MTX ($r=0.618; p=0.002$; 95% confidence interval, 0.254 to 0.829) shown in Figure 1a. Cases between the serum concentration of UA under HDMTX treatment and the $t_{1/2}$ of MTX also showed good positive correlation ($r=0.537; p=0.011$; 95% confidence interval, 0.138 to 0.787, Figure 1b). Increasing serum Cr by HDMTX treatment was related to the $t_{1/2}$ of MTX ($r=0.765; p<0.001$; 95% confidence interval, 0.380 to 0.924, Figure 1c). On the other hand, the dose of MTX per body weight and MTX clearance were poorly correlated ($r=0.201; p=0.249$; 95% confidence interval, -0.142 to 0.501; Figure 1d).

![Figure 1](image-url)

**Figure 1.** a: Relationship between the elevation rate of serum UA and half-life ($t_{1/2}$) of MTX. $r=0.618; p=0.002$; 95% confidence interval, 0.254 to 0.829. b: Relationship between serum UA of post-HDMTX and $t_{1/2}$ of MTX. $r=0.537; p=0.011$; 95% confidence interval, 0.138 to 0.787. c: Relationship between the elevation rate of serum Cr and $t_{1/2}$ of MTX. $r=0.765; p<0.001$; 95% confidence interval, 0.380 to 0.924. d: Relationship between the dose of MTX and $t_{1/2}$ of MTX. $r=0.201; p=0.249$; 95% confidence interval, -0.142 to 0.501. Elevation rate was calculated by dividing the value of post-HDMTX by the value of pre-HDMTX. Statistical analysis was performed by Fisher’s r to z test.
DISCUSSION

We present the results of a retrospective study of the relationship between chemical parameters and MTX pharmacokinetics following HDMTX chemotherapy. MTX treatment significantly increased serum UA, ALT, AST, total protein, total bilirubin and Cr. Three case studies have reported that HDMTX treatment induces hyperuricemia, which is known as a symptom of tumor lysis syndrome (TLS) (Bell et al., 1979). TLS is characterized by hyperkalemia, hyperphosphatemia and is followed by massive lysis malignant cells (Baeksgaard and Sorensen, 2003).

Recent studies have revealed that the pharmacodynamics of MTX is mostly controlled by drug transporters. MRPs, organic anion transporter 1 and 3 (Borst et al., 2000; Cha et al., 2001; Takeda et al., 2002; Chan et al., 2004). Indeed, Cha et al., 2001 reported that uric acid inhibited the activity of organic anion transporter 3. In an in vivo study, MTX clearance was decreased in hyperuricemic rats (Habu et al., 2003). A correlation between the serum concentration of UA treated with HDMTX and t 1/2 of MTX was also observed in this study.

In conclusion, this retrospective study suggests that HDMTX chemotherapy induces hyperuricemia. The delayed excretion of MTX in HDMTX chemotherapy might be responsible for the inhibition of transporter activity by increased uric acid in serum.

REFERENCES


The objective of the study was to survey the present level of consultation with physicians and the instruction of patients concerning drug-drug and drug-food interactions identified at community pharmacies in Japan. The study was conducted by questionnaire with 716 community pharmacies being sent a questionnaire; some 277 responses were received.

Sixty-three per cent of responders reported that they consulted the prescribing physician when medicines such as ciprofloxacin and ketoprofen were prescribed with 67% contacting them when pimozide and erythromycin or clarithromycin were prescribed. Eighty-two percent of pharmacists consulted the physician or instructed the patient when cefdinir and an iron product were prescribed concurrently. Seventy-nine, 95, 69 and 94% instructed patients to avoid the concomitant intake of felodipine and grapefruit juice, nifedipine and grapefruit juice, norfloxacin and milk and triazolam and alcoholic beverages, respectively. In contrast, varied instructions were given to patients when combinations such as amlodipine and grapefruit juice were observed (53% said to avoid, while 39% took no action. Likewise for an iron product and green tea (48% said avoid but 35% failed to take action) and fexofenadine and grapefruit juice (36% noted the interaction but 51% did not).

Variability of instructions given to patients was also observed for medicines that showed different consequences of a drug interaction among similar compounds, or when there was a difference between published experimental data and the description provided on the package insert. This variability in responses to the same drug interaction by different community pharmacists is likely to be confusing to patients and action is therefore necessary to overcome this problem.

**Keywords:** drug-drug interactions, drug-food interactions, consultation with physician, instructions to patient, community pharmacy.
INTRODUCTION

Numerous studies on drug-food interactions have been performed since Bailey et al. (1991) reported the interaction of citrus juices with felodipine and nifedipine, and a great deal of new information has become available to pharmacists in recent years. Indeed, new information about drug-drug interactions appears almost every day. Pharmacists consult with physicians and instruct patients according to their own criteria of importance when they detect pharmaceutical administration problems in the prescriptions presented at community pharmacies for dispensing. Such criteria are usually based on their personal knowledge and information provided or supervised by the government, such as details included in package inserts. However, package inserts are not generally renewed as soon as new experimental data comes to light. Furthermore, the quality and quantity of knowledge about drug interactions varies among individual pharmacists. Therefore, the criteria by which physicians are consulted and/or patients are instructed, are likely to vary widely among pharmacists. Consequently, their response to an interaction may vary when a prescription is received which includes two or more medicine(s) that may lead to a drug-drug or drug-food interaction.

Descriptions on package inserts concerning drug interactions may include the words “should not be used together” and “should be used with caution”. When medicines are identified that “should be used with caution”, pharmacists have to be judgemental as to whether they should contact the prescribing physician and/or instruct the patient accordingly. Clearly, pharmacists are required to consult the physician when a prescription includes medicines that categorically should not be used together.

In this study, we surveyed community pharmacists about whether or not they would consult with the prescribing physician and/or provide suitable instructions to patients if they received prescriptions that included ten combinations of medicine(s) which would result in a drug-drug or drug-food interaction.

METHODS

The study was conducted in June, 2005. Questionnaires were sent to 716 community pharmacies belonging to the Pharmaceutical Association of Kagoshima Prefecture in Japan. A total of 277 responded, giving a response rate of 39%. The questionnaires asked about the reactions of pharmacists when they received prescriptions including medicine(s) known to result in drug-drug or drug-food interactions. The list of drug-drug and drug-food interactions and whether the interactions were included on package inserts are presented in Table 1.

RESULTS

Drug-Drug Interaction

The reactions of pharmacists if they received prescriptions that included medicines identified as “should not be used together” on the package insert are shown in Figure 1. In respect of ciprofloxacin and ketoprofen (Figure 1A) fifty-two per cent of responders indicated that they consulted the physician and recommended avoidance of co-administration. Some 11% contacted the physician without making any recommendation, while 13% stated they did not consult the physician but did

### Table 1. The combination of drug-drug and drug-food interactions studied and the mentioned interaction on the package insert.

<table>
<thead>
<tr>
<th>Drug-Drug Interaction</th>
<th>Warning on Package Insert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin vs Ketoprofen</td>
<td>Should not be used together</td>
</tr>
<tr>
<td>Pimozide vs Erythromycin</td>
<td>Should not be used together</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Should be used with caution</td>
</tr>
<tr>
<td>Cefdinir vs Iron Product</td>
<td>Should be used with caution</td>
</tr>
<tr>
<td>Felodipine vs Grapefruit Juice</td>
<td>Warning on Package Insert</td>
</tr>
<tr>
<td>Nifedipine vs Grapefruit Juice</td>
<td>Should be used with caution</td>
</tr>
<tr>
<td>Amlodipine vs Grapefruit Juice</td>
<td>No Mention</td>
</tr>
<tr>
<td>Norfloxacin vs Milk</td>
<td>Should be used with caution</td>
</tr>
<tr>
<td>Triazolam vs Alcoholic beverage</td>
<td>Should be used with caution</td>
</tr>
<tr>
<td>Iron Product vs Green Tea</td>
<td>No Mention</td>
</tr>
<tr>
<td>Fexofenadine vs Grapefruit Juice</td>
<td>Should be used with caution</td>
</tr>
</tbody>
</table>

...
instruct the patient to take the medicines at particular intervals. Just one per cent neither consulted the physician or gave any instructions to the patient. Most of the others (23%) had never received a prescription that included the medicines in question. **Figure 1B** shows the responses for pimozone and erythromycin or clarithromycin. A similar tendency was observed in the case of ciprofloxacin and ketoprofen. Fifty-seven percent of responders consulted the physician and recommended that co-administration should be avoided while 10% consulted but without making any recommendation. Some six per cent did not consult the physician but did instruct the patient while one per cent neither consulted or instructed the patient. **Figure 2** shows the reaction of pharmacists after receiving a prescription for cefdinir and iron products. The concomitant ingestion of these medicines has been described as “should be used with caution” on package inserts. About one-half of the responders (51%) answered that they instructed the patient to take the two at intervals without consulting the physician. Thirty-one percent answered that they consulted the physician, with 20% having recommended avoiding co-administration. Four per cent of responders had not consulted the physician and had not provided any instructions to their patient.

**DRUG-FOOD INTERACTIONS**

Instructions to patients concerning the intake of grapefruit juice when dihydropyridine calcium antagonists are prescribed are illustrated in **Figure 3**. When felodipine is prescribed, 69% of the responders instructed patients to avoid grapefruit juice using both verbal and written information, followed by 10% who instructed either verbally or with written information (**Figure 3A**). Only two per cent of responders failed to mention the interaction with grapefruit juice. **Figure 3B** shows the case of nifedipine. Some 84% of responders instructed patients both verbally and with written information while 11% did so either verbally or with written

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**Figure 1.** Reaction of pharmacists after they received a prescription which included medicines listed as “should not be used together” on the package insert. A: Ciprofloxacin and Ketoprofen, B: Pimozone and Erythromycin or Clarithromycin.
information with just one per cent not mentioning an interaction. Data for amlodipine is illustrated in Figure 3C. The responders who gave both verbal and written information accounted for 38%, with 15% giving either verbal or written information. In contrast to the above two medicines, those who failed to mention this interaction comprised 39% of respondents.

The results for medicines which have to be used with caution due to possible interactions with certain beverages are summarized in Figure 4. For example, the case of norfloxacin and milk is illustrated in Figure 4A. When norfloxacin is prescribed, some 45% of responders instruct their patients to avoid concomitant milk both verbally and with written information, while 24% instructed them either verbally or with written information. Ten per cent of responders failed to mention this milk interaction. Figure 4B shows the results for triazolam and alcohol. When triazolam was prescribed, 82% of responders instructed their patients to avoid the intake of alcoholic beverages both verbally and in writing, while 12% instructed them either verbally or with written information. No responder failed to identify this interaction. Figure 4C shows the data for iron products and green tea. When an iron product is prescribed, 31% of pharmacists instructed their patients to avoid drinking green tea both verbally and in writing, 17% instructed them either verbally or in writing, while 35% of the responders failed to mention this interaction.

The level of instruction by pharmacists regarding the concurrent intake of grapefruit juice and fexofenadine is illustrated in Figure 5. Some 36% of responders instructed their patients to avoid the intake of grapefruit juice, however, 51% of responders failed to mention this interaction. Of the 36% who instructed their patients to avoid the intake of grapefruit juice, 21% instructed them both verbally and in writing, while 15% provided either verbal or written information.

**DISCUSSION**

Many drug-drug and drug-food interactions have been reported and are identified on package inserts of medicines as either “should not be used together” or “should be used with caution”. When medicines that should not be used together are indeed prescribed together, pharmacists are generally required to consult the prescribing physician. However, when medicines that should be used with caution are prescribed together, the reaction of individual pharmacists is likely to vary depending on their personal judgment.

The co-administration of ciprofloxacin and ketoprofen carries the risk of inducing convulsions (Hattori et al., 1998), while the co-administration of pimozide and erythromycin or clarithromycin may cause QT interval prolongation (Dresser et al., 2000; Flockhart et al., 2000). For these reasons, the
interaction between these medicines has been classified as “should not be used together”. In the present study, 63% of responders concerning the former combination and 67% for the latter, answered that they did in fact consult with the physician. In other words, the majority of community pharmacists are correctly carrying out their professional responsibility as the safety managers of these medications. However, some 14% for the former and 7% for the latter, failed to contact the physician and clearly are in breach of their professional responsibility as health care providers.

When cefdinir and iron products, such as ferrous sulfate, sodium ferrous citrate and ferrous fumarate, are administered concomitantly, the absorption of cefdinir is impaired (Ueno et al., 1993; Miyashita et al., 1999). This drug interaction between cefdinir and iron products has been classified as “should be used with caution” in the package inserts of these medicines. For this reason, the concomitant ingestion of these medicines should be avoided, or the iron product should be taken at least 3 hours after the administration of cefdinir. As for the actual response of pharmacists to this interaction, 51% of the responders said that they instructed the patient accordingly, followed by 31% consulting with the prescribing physician. In total, 82% of the responders answered that they made attempts to avoid the concomitant administration of these medicines, with just four per cent of community pharmacists failing to take any action to avoid this interaction. Thus, with regards the concomitant use of cefdinir and iron products, the overwhelming majority of pharmacists acted responsibly to avoid this interaction taking place.
The interaction between grapefruit juice and dihydropyridine calcium antagonists has been widely reported in recent years. The grapefruit juice leads to a dramatic increase in the area under the concentration-time curve (AUC) of felodipine by Bailey et al., (1991) reported a 251% increase while 285-334% was reported by Edgar et al., (1992), with a 135% for increase for nifedipine (Bailey et al., 1991), against 202% by Sigusch et al., (1994), and 109% by Azuma et al., (1998) when compared to controls. These interactions between grapefruit juice and felodipine or nifedipine are classified as “should be used with caution” on package inserts, and the intake of grapefruit juice has been recommended to be avoided during the taking of these medicines. Some 95% of pharmacists who received a prescription that included felodipine or nifedipine answered that they instructed patients to avoid drinking grapefruit juice, either verbally and/or in writing. In contrast, grapefruit juice has no appreciable effect on amlodipine pharmacokinetics. When amlodipine is administered with grapefruit juice, the increase in the AUC of the drug was found to be only between 114% (Josefsson et al., 1996) and 108% (Vincent et al., 2000) when compared with controls. As for amlodipine, the interaction with grapefruit juice is not mentioned on its package insert, and the reactions of pharmacists were found to be divided into two groups. Fifty-three percent of the responders answered that they instructed the patient to avoid grapefruit juice, verbally and/or in writing, with 39% responding that they did not mention a possible interaction with grapefruit juice.

The absorption of norfloxacin is known to be impaired by the concomitant intake of dairy products, such as milk (Kivisto et al., 1992; Motoya et al., 1997) while the administration of ethanol has been reported to increase the AUC of triazolam and to show greater psychomotor impairment after the
intake of this combination than after either drug alone (Dorian et al., 1985). Such interactions between norfloxacin and milk and triazolam and alcoholic beverages have been classified as “should be used with caution” on package inserts. Sixty-nine percent of responders answered that they instructed patients who were prescribed norfloxacin to avoid the concomitant intake of milk, while 94% instructed patients who were prescribed triazolam to avoid alcoholic intake either verbally and/or with written information. Some 10% of responders did not instruct patients about the interaction with norfloxacin, while no pharmacists failed to point out that triazolam should not be taken with alcohol. In contrast, a serious discrepancy was observed for the interaction between iron products and green tea. Tea drinking has long been thought to impair iron absorption (Watanabe et al., 1968; Disler et al., 1975; De Alarcon et al., 1979). However, data suggesting that tea drinking does not affect the absorption of iron on anemia therapy has also been reported (Harada, 1986; Motoya et al., 1989). In the description on the package insert of iron products, the drinking of beverages containing tannins, such as tea, is recommended to be avoided. As for counseling by community pharmacists, some 48% of responders answered that they instructed the patient to avoid the concomitant intake of iron products and tea, while 35% failed to mention this possible interaction. This discrepancy is likely to result from differences between published experimental data and information provided in the package insert.

As described above, grapefruit juice has been well documented to substantially enhance the bioavailability of some drugs, and the effect is likely to be mediated by an interaction with cytochrome P450 or with active transporter P-glycoprotein. On the other hand, fruit juices, including grapefruit juice, orange juice and apple juice, have been found to inhibit the bioavailability of fexofenadine. This effect of juices is considered to be mediated via the inhibition of intestinal organic anion transporting polypeptide (Banfield al., 2002; Dresser et al., 2002; Dresser et al., 2005). This interaction has yet to be included in the package insert of fexofenadine. In a clinical setting, 36% of responders instructed patients to avoid the concomitant intake of fexofenadine and grapefruit juice, while 51% failed to mention an interaction. This discrepancy again probably results from the difference between experimental data and the description included in the package insert.

In this study, we surveyed the present state of consultation with physicians and instructions given to patients concerning drug-drug and drug-food interactions in community pharmacies in Japan. As for the interactions classified as “should not be used together”, such as ciprofloxacin and ketoprofen, and pimozide and erythromycin or clarithromycin, and a part of “should be used with caution”, such as cefdinir and iron products, felodipine and grapefruit juice, nifedipine and grapefruit juice, norfloxacin and milk, and triazolam and alcoholic beverages, the majority of responders appeared to consult the prescribing physician or instructed their patients of the potential for a drug interaction to occur. Interestingly, these combinations are those in which
no differences occur between the experimental data and the information provided on the package insert. In contrast, for the interactions between amlodipine and grapefruit juice, iron products and green tea, and fexofenadine and grapefruit juice, considerable differences occur between instructions given to patients. These combinations include medicines which show variable degrees of interaction among similar compounds, or those with a difference between the experimental data and the description of the package insert. Such discrepancies are likely to confuse patients, and therefore a unified approach needs to be taken to ensure that all community pharmacists respond to potential interactions in the same way.

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REFERENCES


Use of a gastro-intestinal model and GastroPLUS™ for the prediction of in vivo performance

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This review describes the use of the TNO Gastro-Intestinal Model (TiM-1), a computer controlled dynamic in vitro simulation of the stomach and the small intestine. It has been used to provide an estimation of the amount of drug that is available for absorption for a model drug product and has indicated where in the gastro-intestinal tract (GIT) the drug could potentially be absorbed. The drug release data has been deconvoluted from the TiM1 concentration/time profile, and used as input into GastroPLUS™ simulations software in order to predict the in vivo drug-plasma profile. The use of the system in conjunction with GastroPLUS™ provides an excellent development tool to predict in vivo performance of oral dosage delivery formulations.

Keywords: Gastro-intestinal model, absorption, oral delivery, GastroPLUS™, dissolution
INTRODUCTION

The upper portion of the GIT comprising of the stomach and small intestine constitutes the major absorption organ of the body. The small intestine is further sub-divided into three distinct compartments: the duodenum, jejunum and ileum. In order to predict the in vivo performance of pharmaceutical drugs and drug products, in vitro testing is required to indicate their behaviour once subjected to the variable environments of the GIT. Traditionally, in vitro pharmacopoeial dissolution tests have been used, mainly for quality control purposes. This type of testing, however, does not reflect the changing and dynamic conditions of the upper GIT. These traditional dissolution techniques may simulate one or more of the conditions found in the GIT by using physiologically relevant fluids/conditions, but not the complete dynamic situation encountered by the drug or drug product in passing through the upper GIT.

A multi compartmental dynamic system has been developed and built by TNO Nutrition and Food Research (Zeist, The Netherlands) (Minekus, Marteau, Havenaar and Huis in’t Veld, 1995; Havenaar and Minekus, 1994). The system is the TNO Gastro-Intestinal Model (TIM1) and is made up of four inter-connected compartments, the stomach, duodenum, jejunum and ileum.

TIM1 mimics various parameters in the upper GIT, namely:

i peristaltic movements.
ii pH control in each individual compartment,
iii secretion of enzyme and enzyme activity,
iv bile salt concentrations,
v gastric emptying and physiological transit times,
vi removal of products of digestion and solubilisation/dissolution.

All of the above parameters can be modified for any type of human subject (infant, elderly, etc), as well as including the incorporation of any meal, to investigate food effects. The model was designed by TNO based on data and studies from human volunteers. The model has proved to be reproducible and consistent with measured in vivo data (Smeets-Peeters, Minekus, Havenaar, Schaafsma and Verstegen, 1999). In pharmaceutical analysis the model can be used as a development tool to aid in the selection of a formulation and/or different properties of a compound. To perform an experiment, the test compound and/or formulation is introduced into the gastric compartment and samples are taken at various time-points as it moves through all the compartments of the system. Samples are subsequently analysed off-line.

The results can be expressed in two ways:

i the concentration of the drug that is available for absorption versus time and

ii the quantitative drug analysis indicating the amounts of drug dissolved and where the drug would be available for absorption.

In addition, a total mass balance can be performed to assess the overall recovery of the drug substance from the product/system. It is important to note that the technique will not predict how a compound will be absorbed in vivo since the drug is removed by the process of dialysis which is only dependent on molecular size and concentration gradient. In vivo processes such as facilitated absorption via transporters, efflux mechanisms, hepatic first pass metabolism etc., cannot be modelled in this in vitro system.

GastroPLUS™ simulation software is a computer programme that is used to model the absorption and pharmacokinetic processes of drugs dosed orally and intravenously in humans and animals.

Each simulation requires the numerical integration of nearly 90 differential equations that represent the well-characterized physical processes that occur during drug transport, dissolution/precipitation, luminal degradation, absorption/exsorption, gut metabolism, hepatic metabolism, renal clearance, excretion, and other clearance mechanisms.

The aim of this experiment was to investigate the potential and reproducibility of the TIM1 to establish in vitro/in vivo relationships (IVIVR) in combination with GastroPLUS™ simulation software. An immediate release (IR) tablet formulation containing 20mg paroxetine
hydrochloride hemihydrate (PHCl) (as the free base equivalent), was chosen as a model compound and formulation. PHCl is a BCS Class I compound with good aqueous solubility and permeability.

**TNO GASTRO-INTESTINAL MODEL (TIM-1)**

The model comprises of four compartments representing the stomach and the three sections of the small intestine; duodenum, jejunum and the ileum. (Figure 1). Each compartment is separated by a set of valves which allow the controlled passage of contents via a pulse from one compartment to another. This movement of contents controls gastric emptying and ileal delivery as described by Elashoff et al.

Additionally, the movement is controlled by level sensors attached to each section of the small intestine compartments, which indicate when a pulse is required to the next compartment. Each compartment has two sections which contract alternately simulating peristalsis and water jackets which maintain a temperature of 37°C to mimic body temperature. By the use of a pre-defined protocol, pH profiles are set for each compartment and the model maintains these profiles by automatically secreting acid or base as required. Physiological secretions are introduced to the various compartments namely, pepsin, lipase, electrolytes, pancreatin and bile salts (see Figure 1). Hollow fibre membranes are fitted to the jejunal and ileal sections. The contents of each compartment are continuously washed over the fibres via a counter-current of electrolyte and any drug that is in solution and has come into contact with the fibres is removed and collected.

**METHODS**

A single 20mg PHCl tablet formulation was introduced into the gastric compartment. In order to simulate the standard adult GIT conditions after the intake of water without food a standard ‘fasted’ meal was used which comprised of 10g residual gastric juices, 100ml pH 7.0 citrate buffer and a 170ml glass of water. The pH of the stomach compartment at the start of the experiment was 4.5.

A fasted protocol was utilised which had a fast gastric emptying half life of 30 minutes (i.e. half of the stomach contents emptied in 30 minutes) and which continued at this rate until the compartment was empty. The total run time of the experiment was 6 hours and samples were taken from the jejunum, ileum and at the end of the ileum compartment (which corresponds to delivery to the colon).

At the end of the experiment all the residues remaining in the model were removed and analysed by HPLC in order to calculate the total mass balance of the drug. The experiments were performed in duplicate to assess the reproducibility of the model.

![Figure 1. Schematic diagram of TIM1 secretions, sampling points, dialysis systems, etc.](image-url)
WAGNER-NELSON DECONVOLUTION AND GASTROPLUS™ SIMULATION

The TIM1 concentration/time curves can be defined as representing the summation of two processes, namely the release/“absorption” of the drug from the formulation in the TIM1, and the “elimination” of the drug into the dialysis units as described above. The dissolution of the formulation can therefore be deconvoluted from the TIM1 profile using the Wagner-Nelson method (Wagner and Nelson, 1964) if we assume that the release/“absorption” process happens simultaneously in the TIM1, i.e. as soon as the drug is released from the formulation it dissolves and passes across the dialysis membrane driven by the concentration gradient. In this case, the deconvoluted dissolution curve can be equated to the absorption rate that would normally be calculated using the Wagner Nelson method from a pharmacokinetic plasma concentration profile. This is not unreasonable since the dialysis fibres are simply passive filters with a molecular weight cut-off of around 6,000 and they are designed to provide highly efficient filtration rates for dialysis purposes.

The elimination rate from the TIM1 was determined from the appropriate number of time-points at the end of the concentration/time curve, i.e. after the dissolution from the formulation was considered to be complete. This estimated elimination rate was then used to calculate the dissolution rate from the TIM1 profile using the Wagner Nelson method.

The deconvoluted dissolution profile from the TIM1 was used as the input rate of the drug from the formulation for the GastroPLUS™ model that had been compiled for PHCl using the known physicochemical and PK parameters of this drug, e.g. pH/ solubility profile, effective human permeability, volume of distribution and clearance, number of PK compartments, etc.

RESULTS AND DISCUSSION

The PHCl tablets disintegrated very quickly within the first five minutes of the experiment and particles could be seen to be moving through the system from one compartment to another as a consequence of the gastric delivery and intestinal pulsing.

Figure 2 shows the concentration of PHCl in µg/ml available for absorption versus time for both replicates. These data are derived from the concentration samples taken from the jejunal and ileal dialysis lines for the total duration of the experiments. The individual concentration values are then plotted. The curves are in good agreement with each other, demonstrating the excellent reproducibility of the model.

Figure 3 shows that the total amount of drug recovered in solution for the two experiments was 77% and 73% respectively, of the initial dose. Again, demonstrating good experimental reproducibility.
Viewed against the standard criteria for method development, mean recoveries of 75% could be considered as low. However, TIM1 is a semi-quantitative analytical technique utilised as a development tool and not a quality control technique (such as dissolution testing). The performance of the TIM1 model will depend on the drug compound under investigation and how it interacts with the added fluids and the system itself. Drug could be potentially lost in the TIM1 model in many ways, e.g. if the drug is poorly soluble or precipitates out of solution as a function of changes in pH it will result in reduced recoveries; binding could occur to the various tubing or to the hollow fibre membranes.

**GASTROPLUS™**

**Figures 4 and 5** show the predicted (grey line) for each replicate versus measured PK profile (open boxes) for this formulation using the standard USP II dissolution profile and the deconvoluted TIM1 dissolution profile, respectively.

It can be seen that the predicted profile derived from the TIM1 deconvoluted dissolution profile provides a much more accurate PK profile estimation than that derived from the USP II dissolution profile. This is particularly noticeable over the first 3 hours where the predicted profile from the USP II dissolution profile differs by some 1.5 hours from the measured PK profile. It is therefore reasonable to conclude that the TIM1 profile has provided a much closer estimate of the *in vivo* performance of the formulation.

**CONCLUSION**

The TIM1 model has provided an estimate of the amount of drug that is available for absorption for the representative drug product and has indicated where the drug could potentially be absorbed. The analysis has demonstrated the good reproducibility of the model between two replicates. The release data, once deconvoluted, was used as input into the GastroPLUS™ model in order to predict the plasma profile, for a particular compound. The improved PK profile predicted from the deconvoluted TIM1 dissolution demonstrates that this system provides a more accurate estimate of the *in vivo* dissolution that than of the more typical USP II estimate of drug release.

**REFERENCES**


Traditional treatment for colorectal cancer normally involves intravenous chemotherapy, usually 5-fluorouracil (5-FU) with leucovorin, which may be both inconvenient for the patient and costly for the provider. The development of orally available fluoropyrimidines such as capecitabine and uracil-tegafur and the arrival of newer targeted, biological agents is raising the profile of oral anti-cancer therapies. Patients have a preference for oral therapy providing it can be demonstrated that efficacy is not compromised. Recent large trials in patients with metastatic disease or receiving adjuvant therapy indicate that oral capecitabine is at least as effective as i.v. 5-FU. Although there were significantly fewer adverse effects in patients treated with capecitabine, oral therapy did not seem to offer any advantages in terms of quality of life. Most patients preferred to receive oral chemotherapy over the i.v. alternative, particularly if the bolus regimen was being administered in an in-patient setting. In terms of cost effectiveness, although the initial cost of oral drugs may be greater, when treatment and management costs are taken into account prescribing oral chemotherapy reduces costs overall. Most data would support the switch to oral therapy provided that it does not place undue burden on patients and their carers.

**Keywords:** Colorectal cancer, fluoropyrimidines, oral chemotherapy, quality of life, cost effectiveness
INTRODUCTION
Chemotherapy for cancer has traditionally been given to patients intravenously (i.v.). For patients with colorectal cancer this is certainly the case, where the established treatment in the UK has been intravenous 5-fluorouracil (5-FU) with leucovorin. This is given typically as a bolus in the adjuvant setting or as a 48 hour infusion in patients with advanced disease (Meta-analysis Group, 1998). Many cytotoxics, (including 5-FU) cannot be given orally. However, another reason for the durable popularity of treatment that is delivered intravenously may be that it is perceived to be more potent than an oral equivalent and is therefore ‘better’. A further advantage of i.v. medication over oral is that the dose prescribed is administered to the patient without concerns about compliance or absorption.

The big drawback of i.v. treatments is the inconvenience experienced by the patients, who have to either attend the chemotherapy clinic or be admitted to hospital. This can adversely affect the quality of life of patients with metastatic cancer (Payne, 1992). Portable pumps and indwelling venous lines have allowed i.v. treatments to be given in the community to improve patients’ experience (Vinciguerra, Degnan, Scirionto et al., 1986). However, this requires significant resources for the maintenance of the venous lines and management of complications in addition to the cost of their initial insertion and patient education. The reality is that the delivery of i.v. treatment as an in-patient, in the day case unit, or in the community can be inconvenient and costly.

Oral treatments for cancer are becoming more established in the management of a wide range of malignancies. Oral formulations of classical cytotoxics like cyclophosphamide, chlorambucil and etoposide have been available and in use for a long time. However, the arrival of newer “targeted” drugs like imatinib in chronic myeloid leukaemia and gastro-intestinal stromal tumours has been an important factor in raising the profile of oral anti-cancer therapies.

For patients with metastatic colorectal cancer, regimens containing infusional intravenous 5-FU and leucovorin are superior to bolus treatment with the same drugs (Meta-analysis Group, 1998). The development of orally available fluoropyrimidines like capecitabine and uracil-tegafur (UFT) has sought to exploit the better outcomes seen after more extended periods of exposure to 5-FU. As tablets, they also have the potential to reduce or avoid some of the problems and costs associated with i.v. chemotherapy. This article will concentrate on the use of oral fluoropyrimidines as single agents where the contrast with i.v. treatment is most marked.

ARE ORAL FLUOROPYRIMIDINES AS EFFECTIVE AS I.V. 5-FU IN PATIENTS WITH CRC?
Patients have a definite preference for oral over i.v. therapy. This was shown in a questionnaire-based study of theoretical treatments with equivalent efficacy (Liu, Franssens, Fitch, Warner, 1997). This preference for oral therapy diminished if it was described as less effective than i.v. treatment. So, before offering patients oral treatment it is important to demonstrate that the benefits of oral chemotherapy are not at the expense of efficacy.

Two randomised phase III studies compared oral capecitabine given daily for 14 days and repeated every 3 weeks with bolus i.v. 5FU using the Mayo Clinic regimen of treatment days 1 to 5 repeated every 4 weeks (Hoff, Ansari, Batist et al., 2001; Van Cutsem, Twelves, Cassidy et al., 2001). Both studies demonstrated that capecitabine was at least as effective as 5-FU with superior response rates and equivalent time to progression and overall survival (Table 1). Toxicity profiles were also significantly different for the oral treatment. A combined analysis of these European and American data (Cassidy, Twelves, Van Cutsem et al., 2002) showed that capecitabine required fewer dose reductions and that reducing dose for toxicity appeared not to impact on efficacy, supporting the capecitabine dose reduction strategy (Roche Xeloda® product details). The situation is somewhat different for UFT. Again, two large randomised studies have been published and said to show equivalence with 5-FU (Carmichael, Popiela, Radstone et al., 2002; Douillard, Hoff, Skillings et al., 2002). However, the oral treatment performed less well in these studies. Response rates appeared lower with UFT than 5-FU, but this
There have been no randomised comparisons of capecitabine and UFT. Nor have there been randomised trials of an oral fluoropyrimidine versus infusional 5-FU. An indirect comparison can, however, be made since the Mayo regimen was the control arm in randomised trials with the 48 hour de Gramont (de Gramont, Bosset, Milan et al., 1997) and 24 hour AIO (Schmoll, Kohne, Lorenz et al., 2000) infusional 5-FU regimens. Both infusional regimens achieved higher response rates, with a modest improvement in time to progression (TTP) but no significant survival benefit compared to bolus i.v. 5-FU. Taken together, these data suggest that any differences between capecitabine and infusional 5-FU in terms of efficacy are unlikely to be clinically significant.

Capecitabine has been approved worldwide, but UFT has not been approved in the United States. In the UK, the National Institute for Clinical Excellence (NICE) have considered the evidence and published guidance in May 2003 saying “capecitabine or tegafur with uracil (and folic acid), to be taken by mouth, should be among the first options considered for a person with metastatic colorectal cancer” (www.nice.org.uk).

With evidence that oral chemotherapy is both effective, popular and requires fewer visits to hospital in the advanced disease setting, the application in the adjuvant setting was evaluated. The X-ACT study compared bolus 5FU/leucovorin using the Mayo clinic bolus 5-FU regimen with oral capecitabine in nearly 2000 patients who had Dukes C (i.e. node positive) colon cancer (Twelves, Wong, Nowacki et al., 2005). Capecitabine was at least equivalent to the i.v. treatment. Relapse free survival was significantly superior in patients randomised to capecitabine and multivariate analyses suggested that efficacy was indeed superior in patients treated with capecitabine. A similar trial compared UFT with bolus 5-FU but in patients with node positive or negative disease. Preliminary results suggested no significant differences in efficacy between the two regimens but no indication that the oral regimen was more effective (Wolmark, Wieand, Lembersky et al., 2004).

Taken together, the results of large trials in patients with metastatic disease or receiving adjuvant therapy, indicate that oral capecitabine is at least as effective as i.v. 5-FU.

### Table 1. First line oral chemotherapy compared to i.v. bolus 5FU/FA in metastatic CRC

<table>
<thead>
<tr>
<th>Oral drug</th>
<th>Reference</th>
<th>Response rate</th>
<th>TTP (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>5-FU</td>
<td>Van Cutsem et al (2001) (n=602)</td>
<td>18.9% 15%</td>
<td>5.2 4.7</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>5-FU</td>
<td>Hoff et al (2001) (n=605)</td>
<td>24.8%* 15.5%</td>
<td>4.3 4.7</td>
</tr>
<tr>
<td>UFT</td>
<td>Carmichael et al (2002) (n=380)</td>
<td>10.5% 9.0%</td>
<td>3.4 3.3</td>
<td>12.2 10.3</td>
</tr>
<tr>
<td>UFT</td>
<td>Douillard et al (2002) (n=816)</td>
<td>11.7% 14.5%</td>
<td>3.5 3.8</td>
<td>12.4 13.4</td>
</tr>
</tbody>
</table>

*p < 0.05
HOW DO TOXICITY AND QOL COMPARE WITH ORAL AND I.V. TREATMENT?

The same trials that give insights into the relative efficacy of i.v. and oral fluoropyrimidines also allow comparisons of toxicity.

In patients with metastatic disease, capecitabine caused significantly less diarrhoea, nausea, stomatitis and alopecia than bolus 5-FU (Hoff, Ansari, Batist et al., 2001; Van Cutsem, Twelves, Cassidy et al., 2001); findings were similar with UFT/LV (Carmichael, Popiela, Radstone et al., 2002; Douillard, Hoff, Skillings et al., 2002). The two infusional regimens were also significantly better tolerated than bolus 5-FU (de Gramont, Bosset, Milan et al., 1997; Schmoll, Kohne, Lorenz et al., 2000). The only exception was hand-foot syndrome, which is seen more frequently with capecitabine than either UFT/LV or 5-FU. Quality of life was studied using validated tools in two of the phase III trials in metastatic disease (Carmichael, Popiela, Radstone et al., 2002; Douillard, Hoff, Skillings et al., 2002). These trials were comparing UFT/LV with bolus 5FU. Despite the toxicity profiles in both studies favouring the oral drug, one trial found no difference in QoL using the FLIC questionnaire (Douillard, Hoff, Skillings et al., 2002). The other found a significant difference in favour of the intravenous treatment using the EORTC QLQ-C30 (Carmichael, Popiela, Radstone et al., 2002). The trials comparing capecitabine and 5-FU did not formally report QoL. The pattern of toxicity with capecitabine in the adjuvant setting was the same as in advanced disease. There was no difference in global health status on the QoL questionnaire, but there were significantly fewer adverse events in patients treated with capecitabine (Scheithauer, McKendrick, Begbie et al., 2003).

DO PATIENTS PREFER ORAL TO I.V. MEDICATION?

Having established that patients prefer the idea of oral chemotherapy in comparison to an equally effective i.v. alternative (Liu, Frannssen, Fitch, Warner, 1997), the reality has been tested in patients with cancer in two recently published cross-over studies with UFT (Borner, Schoffski, de Wit et al., 2002) and capecitabine (Twelves, Gollins, Grieve et al., 2006). The design of these two studies in patients receiving first-line therapy for metastatic disease was similar. Patients were randomised to an i.v. 5-FU regimen or the oral fluoropyrimidine for their first cycle of treatment and for the second cycle they received the alternative treatment. They were asked to express a preference for one of the treatments before and after receiving the two different chemotherapies; subsequently they then continued to receive the preferred therapy. In the UFT study of 37 patients (Borner, Schoffski, de Wit et al., 2002) 5-FU was given using the Mayo clinic regimen. In the larger capecitabine study of 94 patients (Twelves, Gollins, Grieve et al., 2006) there were 3 comparators; each investigator selected the Mayo Clinic bolus regimen, infusional de Gramont regimen given as an in-patient, or the same regimen given as an out-patient according to local prescribing habits.

In both these trials, patient preference was not influenced by the sequence of treatment. Oral UFT or capecitabine was preferred to Mayo Clinic bolus 5FU by over 80% of patients after treatment. In the capecitabine study the preference for oral treatment was less marked in comparison with the in-patient (63%) and especially the out-patient (50%) de Gramont regimen. Oral chemotherapy was preferred principally for the convenience of taking a tablet at home. Out-patient infusional chemotherapy was preferred mainly for its side effect profile and scored well for patient satisfaction. Therefore, although most patients prefer oral chemotherapy, the strength of that preference is influenced by which 5-FU regimen is the alternative. Capecitabine is strongly preferred over the more toxic and inconvenient Mayo regimen, but infusional 5-FU given as an out-patient has advantages for others, emphasising perhaps the importance of receiving treatment at home independent of the route of administration.

It is interesting that despite the clear preference of patients for capecitabine or UFT over bolus i.v. 5-FU, QoL did not appear better in patients on oral therapy than those receiving i.v. treatment. However, the QoL tools used in these studies were not designed specifically to assess a patient’s attitude to their treatment or its convenience. It may be that issues directly relating to their disease and side effects of...
treatment dominate patients’ responses to QoL questionnaires. Current QoL questionnaires may not be sufficiently sensitive to detect the impact of factors such as spending more time at home than at the hospital receiving treatment. It may be that new tools could address this issue to allow comparison between treatment modalities.

WHAT ARE THE COST AND RESOURCE IMPLICATIONS OF ORAL THERAPY?

The costs of cancer care and new cancer treatments is a major issue in healthcare today.

For a 24 week course of adjuvant treatment for colon cancer (using the British National Formulary 50 quoted prices) a 1.7m² patient would incur the following drug costs:

**Weekly i.v. bolus 5-FU**

- Folinic acid 20mg/m² = £307.68
- 5-Fluorouracil 370mg/m² = £230.40

**Total = £538.08**

**14 days treatment q21 days capecitabine**

- Capecitabine (1,250mg/m² BD) (56x500mg and 28x150mg) = £130.92 x 8

**Total = £1047.36**

This straightforward calculation appears to show a cost saving for the conventional i.v. treatment. However, when costs of administering i.v. treatment and the management of the increased adverse events seen with the commonly used i.v. regimens are taken into account the picture starts to change. This was demonstrated in the phase III metastatic disease trial comparing capecitabine with bolus 5-FU (Twelves, Boyer, Findlay et al., 2001) where patients on oral treatment required fewer visits to hospital, fewer drugs for the management of toxicity and less hospitalisation with toxicity. A similar analysis of the use of capecitabine in the adjuvant setting has shown a similar saving (Douillard, Twelves, McKendrick, 2004). This is due to fewer clinic visits, fewer hospitalisations and the cost saving predicted for the trend towards improved relapse free survival. In both the metastatic and adjuvant settings oral capecitabine leads to reduced use of resources and cost savings overall.

The NHS R&D health technology assessment programme performed an assessment of capecitabine and UFT in 2003 (www.nchta.org). They looked at cost and resource data published from trials in the advanced setting and also the submissions from Roche (capecitabine) and Bristol-Myers Squibb (UFT) to NICE during their assessment process. They concluded that in the metastatic setting there is a rationale for performing cost minimisation in the comparison as there has been no survival benefit demonstrated between either UFT or capecitabine and the Mayo regimen. Likewise, no survival benefit has been demonstrated with infusional 5-FU over the Mayo bolus i.v. 5-FU regimen so a similar comparison is justified even though infusional 5-FU has never been directly compared with the oral fluoropyrimidines. The assessment found that there were overall savings to be made by prescribing oral chemotherapy in metastatic colorectal cancer. In comparison with bolus 5-FU the saving was £1,461 for capecitabine and £209 for UFT. Compared with out-patient infusional 5-FU the savings were £1,353 and £101 for capecitabine and UFT respectively; the savings were £4,123 and £2,870 respectively compared with inpatient infusional 5-FU. Although these independent analyses confirm the saving to be made with oral fluoropyrimidines, the concern is that in the NHS it is easier to keep track of drug acquisition costs, than to identify and quantify savings made from changes to the process of delivering healthcare.

Another relevant issue arises from recent changes in how NHS trusts in England will be receiving payment from the commissioning Primary Care Trusts. Each visit to the hospital for a consultation and/or treatment will have a national tariff that the Trust can charge. If they provide adjuvant colorectal chemotherapy orally instead of i.v. then the number of patient treatment visits falls from 24 to only 8. This is more convenient for the patients, reduces pressure on pharmacy and chemotherapy staff, but may be at the expense of reduced income for the hospital. It is therefore possible that it would be more “economical” for the Trust to stay with an i.v. strategy that is more expensive, because of the income it attracts. This issue has been recognised previously with health funding systems like those in the US, that have tended to penalise out-patient, oral treatment.
**CONCLUSIONS**

Despite the increasing role of combination therapy, both as adjuvant therapy and as treatment for metastatic disease, many patients still receive single agent fluoropyrimidines. For these patients, there is strong evidence to support the use of oral therapy.

Although capecitabine and UFT have not been directly compared, the stronger data support the use of capecitabine as the oral fluoropyrimidine of choice. For patients with metastatic disease capecitabine has very similar efficacy to i.v. 5-FU but in many regards a better toxicity profile, is more convenient and achieves substantial cost savings. In the adjuvant setting, the same benefits are seen with oral fluoropyrimidines, again the data being stronger for capecitabine than UFT. Both UFT and capecitabine have been combined with irinotecan and oxaliplatin. Most data relate to the incorporation of capecitabine in combination regimens which have efficacy that is very similar to 5-FU based combinations but again with a better toxicity profile and greater convenience. The principal advantage of UFT is that it is not associated with the hand-foot syndrome often seen with capecitabine.

However, the challenges of translating the findings of the clinical trials into everyday practice do need to be considered. Switching to oral chemotherapy transfers responsibility for administration of treatment from trained nursing and medical staff onto the patient and their carers. Compliance and concordance with prescribing instructions become important issues. Historically, the concern has been that poor compliance may lead to under dosing. In relation to the oral fluoropyrimidines, where omitting treatment on days when the patient experiences certain toxicities is a crucial part of management. “Overdosing” may also be an issue. Avoiding problems of this kind requires education of patients, their carers and staff as well as careful monitoring of patients on treatment. Good communication between primary and secondary care is also important with patients receiving their chemotherapy in the community. The savings in time made with oral as opposed to i.v. therapy, especially for nursing and pharmacy staff, may release time for patient education and the possibility of contacting the patient by phone to ensure there have been no problems. These issues have been raised by both medical authors (Cassidy, Twelves, Cameron et al., 1999; O’Neill, Twelves, 2002) and by the British Oncology Pharmacy Association (www.bopa-web.org).

There is increasing use of 5-FU in combination with oxaliplatin or irinotecan both in the metastatic and adjuvant setting. An accumulating body of evidence shows that capecitabine can be combined both with oxaliplatin (XELOX) and irinotecan (XELIRI). The capecitabine-based combinations have very similar activity to their 5-FU-based counterparts but again tend to be better tolerated and more convenient.

An increasing number of targeted, “biological”, therapies are under development. In relation to colorectal cancer, the best examples are bevacizumab which is a monoclonal antibody against circulating vascular endothelial growth factor (VEGF) (Hurwitz, Fehrenbacher, Novotny et al., 2004) and cetuximab an anti-epidermal growth factor (EGF) receptor monoclonal antibody (Cunningham, Humblet, Siena et al., 2004). Both of these agents are given intravenously. However, a number of oral signal transduction inhibitors are in development. Although initial results combining the oral VEGF receptor tyrosine kinase inhibitor, vatalanib, with chemotherapy in patients with advanced colorectal cancer were disappointing in comparison with the i.v. monoclonal antibody bevacizumab (Hurwitz, Fehrenbacher, Novotny et al., 2004), many other oral targeted small molecules are being evaluated. We can appreciate, therefore, that the lessons learnt from the introduction of oral fluoropyrimidines will have a broader relevance in the future.

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A comparison of budesonide administered via Clickhaler® or Pulmicort® Turbuhaler® in paediatric asthma patients

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Aim: When delivering generic therapy, new inhaler devices for asthma are required to demonstrate therapeutic equivalence to their established counterparts. Accordingly, this randomised, open label, parallel group study compared the clinical efficacy and tolerability of budesonide administered to symptomatic asthmatic children via Clickhaler and Turbuhaler dry powder inhalers.

Methods: Children (6-17 years) entered a 2-week run-in period during which they continued their current asthma therapy. Those diagnosed with mild/moderate symptomatic asthma were then randomised to receive budesonide (≤800µg/day), twice daily via Clickhaler or Turbuhaler, for a 4 week period. Daily diary card records of morning and evening peak expiratory flow, asthma symptoms and use of inhaled short-acting β₂-agonist were kept throughout the 6 weeks. Lung function and tolerability data were recorded at three clinic visits (screening, end of run-in and end of treatment). The primary efficacy variable was the change from baseline in mean weekly morning peak expiratory flow.

Results: Of the 262 children entered, 231 were randomised and 195 completed according to the protocol (95 Clickhaler; 100 Turbuhaler). Mean weekly change from baseline for the primary variable, morning peak expiratory flow, was 10.3L/min for Clickhaler and 6.9L/min for Turbuhaler. Analysis of covariance demonstrated clinical equivalence in efficacy between the inhaler groups with a treatment difference of 3.3L/min (95% confidence interval – 2.9 to 9.6). Secondary analyses further supported clinical comparability.

Conclusion: This study in children with mild to moderate symptomatic asthma demonstrated the comparable efficacy of Clickhaler and Turbuhaler dry powder devices for administration of budesonide.

Keywords: Asthma, budesonide, comparable efficacy, corticosteroid, dry powder inhaler
INTRODUCTION

Asthma is currently the most commonly reported long-term medical condition for children in the UK (National Asthma Campaign, 2002). An estimated 4.8 million children in the USA (National Institute of Allergy and Infectious Diseases, 2004) and 1.4 million in the UK receive treatment for asthma and approximately 25 in the UK die each year from the illness (National Asthma Campaign, 2001). The use of inhaled corticosteroids is recommended as the most effective treatment for children with mild to moderate asthma (British Thoracic Society, 2004).

There are many inhaler devices currently available for asthma therapy including metered dose inhalers and dry powder inhalers, and each has advantages and disadvantages. One disadvantage of the conventional press and breathe metered dose inhaler is that children, in particular, can find co-ordinating inhalation with the actuation of the device problematic (De Boeck, Alifier, Wamier, 1999).

The recommended use of valved holding chambers or spacers which combat this problem may be considered inconvenient owing to their size, (Everard, 2000; Brennan, Osman, Graham et al, in press) and therefore breath actuated dry powder inhalers might be a better option for paediatric patients. One disadvantage of the dry powder inhaler is that patients with lower respiratory flow rates, including the very young and the very old, may find it difficult to achieve the inspiratory flow required to activate some dry powder devices optimally (Pedersen, 1995; Pedersen, Mortensen, 1990). The majority of dry powder inhalers, including the Turbuhaler, require an inspiratory flow of 30 to 60L/min in order to aerosolise and deliver the medication to the lung (Borgström, Bondesson, Morén et al, 1994). In contrast, performance of the Clickhaler dry powder device appears to be less dependent on flow rate, (Parry-Billings, Boyes, Clisby et al, 1999) and recent studies have shown that children as young as 3 years of age are able to generate sufficient inspiratory flow to operate the device effectively. (Iqbal, Ritson, Buck et al, 2003; Parry-Billings, Birrell, Oldham et al, 2003) The Clickhaler (Figure 1) is operated simply by depressing a button on the top of the device. It also has a dose counter, and locks out after the final dose, preventing use of the device when empty. The Turbuhaler (Figure 1) is operated using a twist action and is a convenient size to carry. Both devices are easy to use. (Iqbal, Ritson, Buck et al, 2003; Hilton, 1990)

The inhaled corticosteroid budesonide has now been formulated in the Clickhaler, and has shown a comparable pharmacokinetic profile to the Turbuhaler in adult volunteers, (Godfrey, Buck, Ellis, 2002) and equivalent clinical efficacy and tolerability in adult asthma patients. (Parry-Billings, Ayres, James et al, 2003)

The present study was undertaken to compare the clinical effectiveness, tolerability, and acceptability of budesonide administered via the Clickhaler and Turbuhaler dry powder inhalers in paediatric patients with mild to moderate symptomatic asthma.

METHODS

This was a 6-week multicentre, randomised, open label, parallel group study of children aged 6-17 years with mild to moderate symptomatic asthma. The study comprised a 2-week run-in period and a 4-week treatment period, and included 3 clinic visits (screening, end of run-in, and end of treatment). Twenty-seven hospital and general practitioner centres took part in the study, which was conducted...
Budesonide inhalers in paediatric asthma

in accordance with the ethical principles originating from the Declaration of Helsinki (1996) and was approved by a Multicentre Research Ethics Committee and the local Ethics Committees. Patients and/or their parents or guardians gave written informed consent at screening (visit 1).

At screening, children were not permitted to take part in the study if they had been treated with leukotriene antagonists in the previous 2 weeks, oral corticosteroids in the previous 4 weeks, or more than 4 courses of oral corticosteroids in the year prior to the study. Any medical history that might impact on the study outcome including a respiratory tract infection in the 4 weeks prior to the study, hypersensitivity to any constituent of the study inhalers, or current seasonal asthma also precluded study participation.

Patients were entered into a 2-week run-in period, during which they continued to use their current asthma therapy and kept daily diary cards. These were collected at the end-of-run-in-visit, when clinic lung function, vital signs and adverse events were also recorded. These baseline data were used to select patients eligible for randomisation to study treatment.

Children were eligible to continue the study if a clinical diagnosis of mild to moderate asthma was confirmed at visit 2 by evidence of at least 15% reversibility of either forced expiratory volume in the first second (FEV₁) or peak expiratory flow (PEF) after treatment with an inhaled short acting β₂-agonist; and/or diurnal variability of PEF of at least 15% on 7 or more days during the 2 week run-in period; and/or asthma symptoms during at least 4 days or nights during the run-in period; and documented evidence of clinical improvement with anti-asthma medication. Eligible patients were immediately randomised to receive twice daily doses of budesonide (≤800µg/day; 100, 200, or 400µg/actuation) via either the Clickhaler (Innovata Biomed Ltd, UK) or Pulmicort Turbuhaler (AstraZeneca plc, UK) dry powder inhalers, for a period of 4 weeks. The dose of budesonide was determined by the investigator on an individual patient basis. If the patient’s current therapy included an inhaled corticosteroid other than budesonide, this was replaced by the study treatment for the duration of the 4-week treatment period. All children had to demonstrate the ability to use the randomised device after instruction.

Throughout the study, morning and evening PEF, use of inhaled short-acting β₂ medication, and asthma symptoms were recorded daily by the children or their parents on diary cards. Specific symptoms (cough, wheeze and breathlessness), overall daytime, overall night-time, and night-time waking symptoms were rated on an 11 point scale (0 = none/best ever, 10 = severe/worst ever). Lung function (FEV₁, forced vital capacity [FVC], and PEF), and vital signs assessments were repeated at the final clinic visit. Asthma exacerbations and any adverse events were also assessed at this visit from diary card records. Daily use of the study inhalers was recorded on the diary card to assess compliance.

Patient acceptability of the study device was evaluated from questions asked at visit 3. Each child was asked to score the randomised device from 1 to 5 (1 = worst, 5 = best) regarding ease of use, shape of the mouthpiece, dose counter, overall size and shape, hygiene, and awareness of having taken the dose. Investigators were asked to assess the devices for ease of training and assessment of compliance, using the same scoring system. Scores were then compared between treatment groups.

Statistical methods

Data from those patients who completed the study according to the protocol were included in the efficacy analysis. Data from all randomised patients were included in the tolerability analysis. Repeated measures analysis of covariance (ANCOVA) was the main statistical test for efficacy, with diary card morning PEF as the primary variable. Tolerability data for all randomised patients were summarised, considered on an individual basis, and examined for any clinically significant values. Acceptability of inhaler device was compared between the groups using the Wilcoxon rank-sum non-parametric test.

Mean weekly diary card data from the 2-week run-in period and clinic visit 2 data were used as the baseline for their respective efficacy variables.
Changes from baseline in mean weekly data were compared by repeated measures ANCOVA with factors for inhaler, dose of budesonide at randomisation, week, inhaler-by-week, inhaler-by-dose, and inhaler-by-baseline interaction, with baseline as a covariate. Non-significant interaction terms were dropped from the model. Clinic lung function was analysed (ANCOVA) as change from baseline to the end of treatment.

Sample size determination was based on previous studies (Hoekx, Hedlin, Pedersen et al, 1996; Stradling, Pearson, Morice et al, 2000; Adler, Anand, Wright et al, 2001) and calculated using a standard deviation (SD) of 25L/min at the 5% significance level and a statistical power of 80% to enable detection of clinically relevant differences between inhaler groups. For the primary variable, the 95% confidence interval equivalence limits were set at ±10L/min.

RESULTS

Of the 262 children screened for the study 231 were randomised to treatment: 116 to budesonide via the Clickhaler and 115 to budesonide via the Turbuhaler. Ninety-five and 100 patients, respectively, completed the study according to the protocol. One patient randomised to Clickhaler did not take any treatment from the device and was excluded from all analyses. Fifteen randomised patients withdrew during treatment (8 Clickhaler, 7 Turbuhaler), owing to adverse event (6), withdrawn consent (3), protocol violation (3), loss to follow-up (2), and failure to meet entry criteria (1). An additional 20 patients completed treatment but were subsequently excluded from the efficacy analysis owing to protocol deviations. Patient demographics and baseline lung function parameters at screening for these patients who completed according to the study protocol (n=195) are shown in Table 1. Seventy-five per cent were using inhaled corti-

---

**Table 1. Demographics at screening.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>mean±SD (range)</th>
<th>Clickhaler (n=95)</th>
<th>Turbuhaler (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.2±3.1 (6-17)</td>
<td>10.3±2.7 (*5-17)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>54/41</td>
<td>55/45</td>
<td></td>
</tr>
<tr>
<td>Number using inhaled steroid (%)</td>
<td>72 (76)</td>
<td>74 (74)</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.1±0.8</td>
<td>2.0±0.6</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.5±1.0</td>
<td>2.3±0.7</td>
<td></td>
</tr>
<tr>
<td>PEF (L/min)</td>
<td>302.1±107.8</td>
<td>286.2±87.9</td>
<td></td>
</tr>
</tbody>
</table>

* one patient was found to be under the age range but still took part in the study.

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**Table 2. Weekly changes in morning and evening peak expiratory flow (PEF L/min) compared with baseline following twice-daily treatment with ≤800µg/day budesonide delivered via the Clickhaler or Turbuhaler dry powder inhalers to paediatric mild to moderate asthma patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline: mean±SD</th>
<th>Weekly change</th>
<th>LS mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clickhaler (n=95)</td>
<td>Turbuhaler (n=100)</td>
<td>Clickhaler</td>
</tr>
<tr>
<td>Morning PEF</td>
<td>314±113</td>
<td>283±83</td>
<td>+10.3</td>
</tr>
<tr>
<td>Evening PEF</td>
<td>318±113</td>
<td>292±84</td>
<td>+10.7</td>
</tr>
</tbody>
</table>

LS = least square, CI = confidence interval.
Table 3. Weekly change in asthma symptom scores and use of inhaled short-acting $\beta_2$ medication following twice-daily treatment with $\leq$800µg/day budesonide delivered via the Clickhaler or Turbuhaler dry powder inhalers to paediatric mild to moderate asthma patients. Symptoms were rated on an 11 point scale (0 = none/best ever 10 = severe/worst ever).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline: mean±SD</th>
<th>Weekly change</th>
<th>LS mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clickhaler (n=95)</td>
<td>Turbuhaler (n=100)</td>
<td></td>
</tr>
<tr>
<td>Overall night-time</td>
<td>1.5±1.9</td>
<td>1.1±1.4</td>
<td>−0.27</td>
</tr>
<tr>
<td>Night-time waking</td>
<td>1.5±1.8</td>
<td>1.0±1.3</td>
<td>−0.35</td>
</tr>
<tr>
<td>Overall daytime</td>
<td>2.1±1.9</td>
<td>1.6±1.6</td>
<td>−0.42</td>
</tr>
<tr>
<td>Cough</td>
<td>1.7±1.9</td>
<td>1.4±1.6</td>
<td>−0.50</td>
</tr>
<tr>
<td>Wheeze</td>
<td>1.1±1.3</td>
<td>0.9±1.2</td>
<td>−0.31</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>1.1±1.4</td>
<td>0.9±1.2</td>
<td>−0.30</td>
</tr>
<tr>
<td>Use of $\beta_2$</td>
<td>11.4±14.0</td>
<td>10.1±12.5</td>
<td>−1.8</td>
</tr>
<tr>
<td>medication (No. of</td>
<td></td>
<td></td>
<td>−2.4</td>
</tr>
<tr>
<td>times per week)</td>
<td></td>
<td></td>
<td>0.6 (−1.6 to 2.8)</td>
</tr>
</tbody>
</table>

LS = least square, CI = confidence interval.

Figure 2. Mean (+SEM) weekly morning peak expiratory flow (L/min) during treatment with $\leq$800µg/day budesonide administered via Clickhaler (n=95) or Turbuhaler (n=100) dry powder inhalers to paediatric patients with mild to moderate symptomatic asthma.
costosteroids as part of their existing therapy before the start of budesonide treatment with no significant differences between the inhaler groups (62% beclomethasone dipropionate, 21% budesonide, 17% fluticasone). Most (90%) patients (84 Clickhaler, 91 Turbuhaler) continued to display asthma symptoms during the run-in period. The mean daily budesonide dose during treatment was 405µg and 398µg for the Clickhaler (n=95) and Turbuhaler (n=100), respectively. Diary card data showed that mean compliance with treatment was ≥95%.

The least square mean weekly change from baseline over the 4-week treatment period for the primary efficacy variable of morning PEF was 10.3L/min for the Clickhaler and 6.9L/min for the Turbuhaler. The mean weekly difference between the groups was 3.3L/min and the 95% confidence interval (–2.9 to 9.6) confirmed comparable efficacy of the two treatments (Table 2). No statistically significant effects were noted for any of the factors in the repeated measures ANCOVA for morning PEF. Mean weekly morning PEF during the 4-week treatment period are shown in Figure 2.

Evening PEF changes during treatment are also shown in Table 2. The least square mean weekly change from baseline was 10.7L/min for Clickhaler and 3.7L/min for Turbuhaler. The mean weekly difference between the groups was 7.1L/min and the 95% confidence interval was 1.1 to 13.1. This difference between treatments was statistically significant (p=0.02) in favour of the Clickhaler. No statistically significant effects, other than the baseline covariate, were shown for any of the factors during repeated measures ANCOVA for evening PEF. Least square mean weekly changes for all asthma symptoms were similar for both devices and all confidence intervals supported device comparability (Table 3). Least square mean weekly change from baseline was used was –1.8 for the Clickhaler and –2.4 for the Turbuhaler. The mean weekly difference between the groups was 0.6 and the 95% confidence interval was –1.6 to 2.8. All clinic lung function parameters were similar for both groups (Table 4).

### Table 4. Clinic lung function (mean±SD) at the start (baseline) and end of twice-daily treatment with ≤800µg/day budesonide via Clickhaler or Turbuhaler dry powder inhalers to paediatric mild to moderate asthma patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clickhaler</th>
<th>Turbuhaler</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>2.2±0.9</td>
<td>2.0±0.7</td>
<td></td>
</tr>
<tr>
<td>end</td>
<td>2.3±0.8</td>
<td>2.1±0.6</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>2.6±1.0</td>
<td>2.3±0.8</td>
<td></td>
</tr>
<tr>
<td>end</td>
<td>2.6±0.9</td>
<td>2.4±0.7</td>
<td></td>
</tr>
<tr>
<td>PEF (L/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>314.6±109.0</td>
<td>295.0±93.2</td>
<td></td>
</tr>
<tr>
<td>end</td>
<td>325.9±110.8</td>
<td>307.5±85.3</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in the first second, FVC = forced vital capacity, PEF = peak expiratory flow.

### Table 5. Acceptability of the Clickhaler or Turbuhaler dry powder inhalers following twice-daily treatment with ≤800µg/day budesonide to paediatric mild to moderate asthma patients. Acceptability was scored from 1 to 5 (1 = worst, 5 = best).

<table>
<thead>
<tr>
<th></th>
<th>Clickhaler best scores %</th>
<th>Turbuhaler best scores %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall ease of use</td>
<td>70</td>
<td>54</td>
<td>0.006</td>
</tr>
<tr>
<td>preparation for use</td>
<td>65</td>
<td>49</td>
<td>0.007</td>
</tr>
<tr>
<td>awareness of dose taken</td>
<td>34</td>
<td>21</td>
<td>0.002</td>
</tr>
<tr>
<td>recording of doses</td>
<td>79</td>
<td>17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Investigators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ease of assessing compliance</td>
<td>67</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Budesonide treatment was well tolerated by the children. There were no statistical differences between the groups for the number of patients reporting adverse events during treatment (50 Clickhaler, 40 Turbuhaler).

The most frequently reported adverse events were recorded by similar numbers of patients in both inhaler groups: aggravated asthma (11 Clickhaler, 10 Turbuhaler), cough (7 Clickhaler, 2 Turbuhaler), pharyngolaryngeal pain (6 Clickhaler, 2 Turbuhaler), and nasopharyngitis (4 Clickhaler, 7 Turbuhaler).

Three serious adverse events were reported during treatment by 3 patients, one of which (aggravated asthma whilst on holiday, Clickhaler) was thought to be possibly related to treatment.

The incidence of asthma exacerbations was low during the run-in period (6 Clickhaler, 8 Turbuhaler). A further 13 exacerbations were experienced in each inhaler group during treatment. Changes in vital signs were unremarkable. No statistical analysis was performed on these data.

Of the eleven questions answered by the children, and the two answered by the investigators, the Clickhaler was significantly better in terms of preparation for use ($p=0.007$), noticeability of dose taken ($p=0.002$), ease of dose tracking ($p<0.001$), overall ease of use ($p=0.006$), and assessing patient compliance ($p<0.001$) (Table 5). The Turbuhaler was not statistically significantly superior for any of the acceptability questions.

**DISCUSSION**

A growing selection of new generic dry powder inhalers is now available for use in asthma management. This class of new inhalers for asthma must demonstrate therapeutic comparability to their existing established counterparts. (Directive 2001/83/EC) Accordingly, this study was carried out to compare the clinical efficacy and tolerability of budesonide administered via Clickhaler and Turbuhaler dry powder inhalers in children with mild to moderate symptomatic asthma. The primary efficacy variable of morning PEF confirmed the comparability of the two devices in this paediatric population. Asthma symptom and tolerability data further supported clinical comparability.

An open, randomised, parallel group study design was employed, based on the design of previous studies comparing inhaled corticosteroids in children (Williams, Richards, 1997) and adults. (Langdon, Capsey and the UK study group, 1994) A 4-week treatment period has also been verified in previous studies as an appropriate period in which to evaluate the efficacy of an inhaled corticosteroid, (Williams, Richards, 1997; Adler, Anand, Wright et al, 2001) with morning PEF as an accepted measure of therapeutic efficacy in asthma. (Reddel, Salome, Peat et al, 1995) A twice-daily dosing regimen was utilised as this is the recommended dosing frequency for paediatric asthma. (British Thoracic Society, 2004) Repeated measures ANCOVA was selected to analyse these data as this method analyses the data over the whole 4-week treatment period to provide a single estimate of the differences between two treatments or devices.

The world-wide prevalence of asthma is increasing by an average of 50% per decade. (O’Connell, 2002) and in the UK it is now the most common disease in pre-school children. (National Asthma Campaign, 2002) Clinicians need to balance the therapeutic advantages of corticosteroids with possible treatment side effects, which include growth suppression, decreased adrenal activity, oropharyngeal thrush, and voice hoarseness. (Kamada, 1997; Skoner, 2002) Systemic side effects can result from the absorption of a proportion of the inhaled or swallowed dose of corticosteroid. (Skoner, 2002) Growth suppression is, however, less likely to occur in children using corticosteroids such as budesonide, owing to its rapid first-pass hepatic metabolism which reduces the extent of systemic exposure. (Pedersen, 2001) To reduce the risks of side effects, and give maximum benefit to patients, it is important to prescribe the minimum effective corticosteroid dose via the most appropriate inhaler for each patient. In addition, it is important that patients comply with their prescribed treatment. Problems associated with metered dose inhalers such as co-ordination of inhalation and actuation, and the size of holding chambers (spacers) may have an impact on patient compliance. (Everard, 2000; Brennan, Osman, Graham et al, in press)
To provide optimal treatment for asthma, regular use of inhaled corticosteroids is recommended. (British Thoracic Society, 2004) Despite routine use by 75% of patients, the majority of patients continued to display asthma symptoms during the run-in period. The improvement in asthma symptoms seen in this investigation following regular study treatment could be the result of using a more effective device throughout the study than during pre-study, improved compliance imposed by study conditions, or the change in treatment from beclomethasone dipropionate (62%) to budesonide during the study treatment period.

The successful delivery of dry powder formulations relies on the degree of inspiratory effort required, and it is important for patients to have access to inhalers that provide optimal drug delivery at achievable flow rates. This is of particular importance for both children and adult patients with respiratory impairment who may not be able to inhale adequately to ensure successful dose delivery from some dry powder devices. (De Boeck, Allifier, Wamier, 1999) Breath actuated dry powder devices are increasingly being used in place of metered dose inhalers, and the Turbuhaler is a well-established reservoir device. The Turbuhaler, however, is dependent on the patient generating inspiratory flow rates of 30-60L/min to deliver the dose effectively, (Borgström, Bondesson, Morén et al, 1994) and provides optimal drug delivery at 60L/min (van der Palen, 2003). Since the Clickhaler is relatively independent of flow rate (Parry-Billings, Boyes, Clisby et al, 1999) and can be operated easily by children (Parry-Billings, Birrell, Oldham et al, 2003) it is a suitable alternative device for the delivery of corticosteroids.

The Clickhaler was found to be significantly better than the Turbuhaler for a number of acceptability questions by patients and investigators suggesting this device may be easier to use. This is supported by a study of adults treated with budesonide who found the Clickhaler to be significantly superior to the Turbuhaler during an acceptability assessment (Parry-Billings, Ayres, James et al, 2003).

Asthma is a growing problem but effective drugs exist to control it such as inhaled corticosteroids and inhaled bronchodilators. Management of asthma, however, is dependent on devices that facilitate optimal delivery and/or distribution, and regular use of these drugs. Previous research has shown that the Clickhaler is an effective device for the delivery of both inhaled corticosteroids and bronchodilators for the maintenance of asthma in children. Adler et al showed that the Clickhaler was equivalent to an MDI during 4 weeks’ beclomethasone dipropionate treatment of mild to moderate paediatric asthma patients (Adler, Anand, Wright et al, 2001). In a similar population, and using a comparable trial design, the Clickhaler was as effective as an MDI for the administration of the bronchodilator salbutamol (O’Callaghan, Everard, Bush et al, 2002). Additionally, a study of children with exercise-induced asthma indicated that the bronchodilator formoterol was clinically equivalent when delivered via the Clickhaler and an MDI. (Gunawardena, Palmer, Das et al, 2003) The results of this study have demonstrated comparable efficacy of the budesonide Clickhaler with the established Turbuhaler device and, combined with previous knowledge, supports the use of the Clickhaler dry powder inhaler in paediatric asthma patients.

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REFERENCES


Budesonide inhalers in paediatric asthma


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