Clinical Therapeutics

Introduction: Oral or intravenous (IV) paracetamol (APAP) is used for mild to moderate pain but has a latency to be effective. When fast relief is required and oral/IV routes are not available because of the patient’s condition, the transmucosal buccal route may be an alternative. A new transmucosal buccal (b) pharmaceutical form of APAP that had been previously assessed in healthy volunteers is studied in patients admitted to hospital for acute pain.

Patients (or Materials) and Methods: A randomized double-blind noninferiority clinical trial (NCT01586143) included 38 patients admitted to the Accident and Emergency Department of Clermont-Fd University Hospital, France, for trauma of the upper or lower limb, and with pain intensity between 4 and 6 on a 0 to 10 numerical scale (NS). Patients were injected at t0 over a 15-minute period with placebo (0.9% saline) or APAP (1 g) and concomitantly, 125 mg of APAP dissolved in 1 mL of an hydroalcoholic solution (HAS) or placebo (HAS only) was applied in the left mucogingival sulcus. Patients were asked not to swallow for 1:30 minutes. NS evaluations were done at t10, t30, t120, and t180 minutes after administration.

Results: Results (mean [SD]) show no significant PID difference between bAPAP and iAPAP, respectively: t10min (–0.9 [1.3] vs –1.3 [1.8]), t30min (–2.0 [1.8] vs –2.4 [1.5]), t120min (–2.9 [1.9] vs –3.3 [1.5]), t180 (–2.1 [2.2] vs –3.4 [1.8]; all P > 0.05).

Conclusion: Transmucosal buccal APAP has a similar analgesic effect than iAPAP in patients admitted to hospital for acute trauma pain of mild to moderate intensity. The mechanism of action of this pharmaceutical form must now be studied further. This attractive alternative to other routes would be useful in situations where oral or IV routes are not available or in vulnerable populations (cancer pain, palliative care, geriatrics) for acute pain paroxysms.

Disclosure of Interest: None declared.

OC029—INTERACTION BETWEEN MYCOPHENOLATE MOPHELT AND TACROLIMUS IN KIDNEY GRAFT RECIPIENTS

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Introduction: The calcineurin inhibitor (CI) tacrolimus remains the mainstay of kidney transplant maintenance immunosuppression. In most patients, it is combined with mycophenolate mofetil (MPA) and corticosteroids. As part of an investigation of effect of drug–drug interactions in the setting of routine care, we investigated the effect of mycophenolate mofetil dose on the kinetics of tacrolimus.

Patients (or Materials) and Methods: We performed a retrospective analysis of TDM measurements in the past 5 years at a single transplant center in the University Hospital in Olomouc, Czech Republic. More than 4000 measurements of trough concentrations (C0) of CIs and MPA were included in the analysis made in 111 male and 70 female kidney transplant recipients (181 in total). Patients were aged 13 to 72 years (average, 45.7). Average time from transplant was 5.6 years (0.4 to 18).

Drug measurements were obtained from the hospital information system, and information on prescription was ascertained from prescription database and patient clinical records (including dosing instructions and specific temporary instructions concerning co-prescription of interacting medication). CI levels were expressed as normalized dose (ND) required to reach a unit concentration and a linear regression model was constructed to quantify effects of various interacting factors (eg, age, sex, prednisone dose, MPA dose, body weight).

Tacrolimus ND = a0-a1 × MPA + a2 × Tx-a3 × ATB-a4 × INTER + a5 × DOSE-a6 × AGE

Where MPA is the dose of mycophenolate mofetil in mg/kg body weight, Tx is time from transplantation in years, ATB is 1 if the patient is treated with an antimicrobial, INTER is 1 if the patient is treated with an interacting antimicrobial, DOSE is the dose of tacrolimus in μg/kg of body weight, and AGE is patient’s age in years.

Results: The constructed model yielded the following statistically significant parameters: The coefficient for MPA dose means that for each 100 mg of MPA there was on average a 0.99 l/kg reduction in the dose of tacrolimus to reach a unit concentration (14%). Other significant factors included time from transplantation, interacting antimicrobials, and age (all, P < 0.001).

Conclusion: Our data from routine clinical practice indicate the presence of a mycophenolate-mofetil and tacrolimus interaction. Some literature reports confirm this interaction, but data are still conflicting, and more studies are needed to confirm its clinical significance.

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OC030—GEMFIBROZIL IMPAIRS IMATINIB ABSORPTION AND INHIBITS THE CYP2C8-MEDIATED FORMATION OF ITS MAIN METABOLITE IN HEALTHY VOLUNTEERS

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Introduction: According to the product information of imatinib, imatinib is mainly metabolized by CYP3A4. Because our recent in vitro findings indicate that CYP2C8 participates in imatinib N-demethylation3 and there are no clinical data concerning the role of CYP2C8 in its metabolism, we studied the effects of the strong CYP2C8 inhibitor gemfibrozil on the single-dose pharmacokinetics of imatinib in healthy volunteers.

Patients (or Materials) and Methods: In a randomized, crossover study, 10 healthy subjects were administered gemfibrozil 600 mg or placebo twice daily for 6 days, and imatinib 200 mg on day 3. The plasma concentrations of imatinib and its main metabolite N-desmethylimatinib (N-DMI) were determined using a liquid chromatography–tandem mass spectrometry system. The pharmacokinetics of imatinib and N-DMI were calculated by noncompartmental analysis. Logarithmic transformation was used for pharmacokinetic variables, and statistical comparisons between the phases were made with the paired t test. Because imatinib may time dependently inhibit its own CYP3A4-mediated elimination,4 the obtained clinical data was then applied to a physiologically based pharmacokinetic (PBPK) model to predict the contribution of CYP2C8 to imatinib metabolism during multiple-dose administration.