Letters to the Editors

Prevalence of factitious hypoglycaemia associated with sulphonylurea drugs in France in the year 2000

Hypoglycaemia presents important diagnostic and therapeutic problems. Severe and repetitive hypoglycaemic episodes without treatment may be difficult to explain. Failure to identify factitious hypoglycaemia may lead to laparotomy or pancreatectomy [1, 2].

To estimate the prevalence of factitious hypoglycaemia due to sulphonylurea drugs in patients with unexplained severe hypoglycaemia, we conducted a prospective study during the year 2000. Hypoglycaemic patients were recruited throughout France. Plasma was assayed for oral hypoglycaemic agents on the clinician's request, using h.p.l.c. with u.v. detection. Fifty-six patients with unexplained hypoglycaemia were recruited. In seven of these patients (five women, two men), a sulphonylurea oral hypoglycaemic agent was detected (Table 1).

Plasma concentrations were usually supra-therapeutic and concentrations up to 15 times the upper limit of the therapeutic range were observed.

In one 45-year-old patient, during hospitalization, we identified glibenclamide concentrations of 529 µg l⁻¹ at 11.00 h (therapeutic concentration 25–50 µg l⁻¹), of 696 µg l⁻¹ at 22.00 h, of 154 µg l⁻¹ at 06.15 h and of 367 µg l⁻¹ at 08.00 h over a 2 day period.

Insulinoma has been suspected in such patients due to continued surreptitious consumption of medication during hospitalization.

Cases of factitious hypoglycaemia from oral hypogly-

caemic agents have been published [1–4], and may be a manifestation of Munchausen's syndrome [5]. Factitious hypoglycaemia due to sulphonylurea drugs should be considered in the differential diagnosis of insulinoma.

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Received •• 2002, accepted 7 August 2002

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Table 1 Plasma concentrations observed.

Hypoglycaemic agent	Maximal concentrations observed	Therapeutic range	Elimination half-life
Glibenclamide (<i>n</i> = 4)	696 µg l ⁻¹	25–50 µg l ⁻¹	5 h–10 h
Glimepiride (<i>n</i> = 2)	418 µg l ⁻¹	300 µg l ⁻¹	5 h–9 h
Gliclazide (<i>n</i> = 1)	2.1 mg l ⁻¹	1.5 mg l ⁻¹	8 h–12 h

Penetration of fosfomycin into the parenchyma of human brain: a case study in three patients

Bacterial brain infections represent life threatening events, often unresponsive to standard antibiotic treatment. Whereas therapeutic failure might be caused by

infections with multiresistant bacteria, the central nervous system (CNS) differs from other infectious loci, since the infection site, i.e. brain parenchyma, is secluded from the rest of the body by the blood brain barrier (BBB), which renders the brain impermeable to many exogenous and endogenous compounds. Therefore, success of antibiotic

therapy is also dependent on the ability of antibiotics to cross the BBB and penetrate the CNS.

Unfortunately, our knowledge about antibiotic CNS penetration in patients is rudimentary and has so far been restricted to single point measurements in brain tumours, intracranial abscesses, or the cerebrospinal fluid (CSF) [1]. Recently, clinical microdialysis (MD) was suggested as a novel method to measure directly antibiotic brain concentrations humans [2]. MD has evolved as an important instrument for the measurement of effect site concentrations of various analytes in different clinical settings, including neurometabolic monitoring in intensive care units [3]. However, the CNS penetration and intracerebral pharmacokinetics of drugs have not yet been routinely monitored [4]. For antibiotics in particular, MD would allow definition of the relationships between effect site pharmacokinetics, namely, those concentrations to which pathogens are directly exposed and clinical response, with possible consequences for current dosage recommendations.

To describe plasma to brain distribution of fosfomycin, a broad spectrum antibiotic with reported favourable penetration characteristics to peripheral tissues [5] and the CSF [6], MD experiments were conducted in three patients. These were a 28 year-old woman with left frontal intracerebral haematoma, a 22 year-old man after severe head injury and cerebral contusions and a 65-year-old woman with subarachnoid bleeding (SAB) and intracerebral haemorrhage. They all needed neurosurgical intensive care treatment and received prophylactic antibiotic medication. The study was approved by the local ethics committee and was performed in accordance with

the Declaration of Helsinki and the GCP Guideline of the EC. The study met the criteria set by the ethics committee for patients who are unable to give consent because of incapacity.

Fosfomycin concentrations in brain interstitium were measured employing commercially available microdialysis brain catheters (CMA 70, CMA, Sweden) after implantation into brain parenchyma of the noninjured frontal lobe in combination with a routinely used ventricular catheter (NMT Neurosciences Implants S.A. Sophia Antipolis cedex, France). The MD catheter was placed with its tip in the white matter, and the system was perfused with Ringer's solution at a flow rate of $1.5 \mu\text{L min}^{-1}$. After equilibration and baseline sampling, 4 g fosfomycin (Fosfomycin[®], Biochemie GmbH, Vienna, Austria) were administered as an i.v. bolus via a central venous catheter. Fosfomycin from dialysates and arterial blood samples, collected in defined intervals up to 6 h, was analysed by gas chromatography [7]. Intracerebral concentrations were calculated from dialysate concentrations as described previously [5]. The ratio $\text{AUC}_{\text{plasma}}/\text{AUC}_{\text{brain}}$ was calculated as a measure of CNS penetration.

In patient 3 intracerebral fosfomycin concentrations could not be quantified. At first sight no definite explanation for this finding could be identified, as the MD catheter was inserted into the noninjured hemisphere. However, transcranial Doppler ultrasound recordings of both middle cerebral arteries indicated severe vasospasm, known to occur frequently after SAB, and a CT scan performed 2 weeks later showed multiple infarctions of both hemispheres in the middle and anterior cerebral

Figure 1 Fosfomycin concentration *vs* time profiles for plasma (▲) and brain tissue (△) following i.v. bolus administration of 4 g fosfomycin to two neurosurgical patients. In the third patient fosfomycin could not be quantified. (The dotted line indicates estimated fosfomycin concentrations in a peripheral tissue based on data from Frossard *et al.* [5]).

artery territory. The patient died 4 weeks after admission with signs of ventriculitis and after having developed refractory intracranial hypertension and cerebral oedema.

Figure 1 depicts fosfomycin concentration *vs* time profiles for plasma and brain interstitium for the other two patients. $AUC_{\text{plasma}}/AUC_{\text{brain}}$ ratios were 4.8 and 13.3 for patient 1 and 2, respectively. Plasma and brain C_{max} values were 606 and 42 $\mu\text{g ml}^{-1}$ (patient 1) and 244 and 12 $\mu\text{g ml}^{-1}$ (patient 2). Patient 1 died from ARDS and septicaemia 10 days after admission, without signs of CSF or cerebral infection. Follow-up of patient 2 was unremarkable.

In the present study BBB transport of fosfomycin was variable. Compared with the almost complete equilibration between plasma and peripheral tissues concentrations [5] (Figure 1, dotted line), interstitial brain concentrations did not equilibrate with corresponding plasma concentrations. However quantifiable cerebral C_{max} values were above MIC values for relevant pathogens such as *Streptococcus pneumoniae* or *Neisseria meningitidis*. Variability in plasma/brain penetration ratios might be explained by the degree to which the integrity of the BBB is disrupted by the underlying disease [8]. Since BBB permeability is not predictable, current dosing is usually based on CSF sampling or empirical data. However, CSF concentrations might differ from actual brain tissue concentrations due to a ventricular-lumbar concentration gradient [1]. Therefore, direct access to the effect site, as provided by clinical MD, is mandatory to relate accurately target site concentrations to clinical effect. Only the patient with cerebral vasospasm, and thus a dramatically reduced capillary exchange surface developed an intracerebral infection. Thus it might be hypothesized that in addition to BBB transport or oedema formation associated with infraction, which would reverse the pressure gradient and the bulk flow of a molecule, the function of the capillary surface area and capillary density might profoundly influence drug pharmacokinetics within human brain parenchyma.

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Does age increase the risk of adverse drug reactions?

Keywords: adverse drug reactions, age, pharmacovigilance, risk factor

In the 6 years from January 1st 1995 to December 31st 2000, 92 043 spontaneous domestic reports of adverse

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Received 2002, accepted 14 May 2002

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drug reactions (ADRs) were recorded in the French pharmacovigilance database. Related to the size of the French population (58.5 millions inhabitants, 1999 National Census) this figure corresponds to an average reporting rate of 2.62 per 10 000 inhabitants per year (2.46 for men, 2.79 for women).

The use of age-specific reporting rates showed (Figure

Figure 1 Age-specific reporting rates (France 1995–2000) before (crude, ◆) and after (adjusted, ■) adjusting for drug consumption.

1) a marked apparent increase in risk with age: the average ADR reporting rate was thus 1.94 per 10 000 inhabitants and per year before 60 years and 5.13 beyond this age ($P < 10^{-6}$). This apparent increase of the risk of ADR with age has been already found by several studies [1–3].

As a reference for drug consumption (prescribed or not, reimbursed or not), we used data of from C.R.E.D.E.S (Centre de Recherche d'Etude de Documentation en Economie de la Santé, Paris) [4]. The C.R.E.D.E.S statistics provided the average number of drug packages bought per person in France in 1998 according to age (in 10 year bands), which allowed computation of age-specific reporting rates adjusted for drug consumption. After adjustment, the relationship with age disappeared (Figure 1). The distribution of reporting rates, previously ranging from 1.05 to 7.48 per 10,000, varied from 2.38 to 4.42 per 10,000, with a peak in the 30–39 year old class.

This confirms the observation previously made by US and European authors: the greater incidence of ADRs in elderly patients observed in unadjusted studies conducted on the basis of spontaneous reports could be in part explained by exposure to a greater number of drugs [5–9].

It should be emphasized that our study was based on averaged risks of adverse drug reactions and did not discriminate either for seriousness or ADR types (e.g. certain types of ADRs, such as gastro-intestinal toxicity, could have a greater probability of occurring in elderly patients while others could be more frequent in younger patients).

Moreover, our results are based on spontaneously reported data and not on the (unknown) actual number of ADR cases in the source-population. Under-

reporting, leading to a marked underestimation of incidence rates, might be thought to be not the same for middle-aged or elderly patients, and if greater in the latter might explain, in part, the absence of difference after adjusting for drug consumption. However, the existence of an age-specific under-reporting is not supported neither by our experience nor the literature.

This study supports the idea that the main factor for the risk of adverse drug reaction is the number of drug treatments and not the age itself.

We are indebted to the Agence Française de Sécurité Sanitaire des Produits de Santé and to the Association Française des Centres Régionaux de Pharmacovigilance for their permission to use the database.

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Received •• 2002, accepted •• 2002

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