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INDUCTION AND INHIBITION OF DRUG ELIMINATION IN CRITICAL CARE PATIENTS AS SHOWN BY PENTOBARBITAL AND METAMIZOL CLEARANCE

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Drug therapy in critically ill patients is often complicated by the high number of drugs given simultaneously (usually 10 - 15) and the insufficiency of organs being important for drug elimination, such as liver and kidneys. Drug interactions may occur based on changes in drug metabolism activity either by enzyme induction or inhibition. These changes may be influenced by severe illness, e.g. renal or liver insufficiency. Determinations of urinary D-glucaric acid and 6ß-hydroxycortisol as non-invasive parameters of drug metabolizing enzyme activity demonstrated that induction in critical care patients occurs primarily when barbiturates or miconazole, an imidazole antifungal agent, are administered (1,2). It was therefore of interest to know how elimination of frequently given drugs such as pentobarbital (Nembutal®) and metamizol (Novalgin®) can be altered in these patients.

METHODS

16 patients suffering from severe head injury were studied during high dose pentobarbital therapy (30 mg/kg/day) to reduce high intracranial pressure. The medication prescribed for continuous administration is summarized in the table. Pentobarbital clearance was determined twice in each patient during steady state by gas chromatography. Metamizol

	Metamizol		Pentobarbital
n =	10	10	16
Creat. Clearance (ml/min/1.73m²)	89.5 ± 31.4	7.1 ± 9.8	n.d.
Digitalis	6	2	5
Cimetidine	1	4	14
Pirenzepine	1	2	12
Penicillines	7	6	8
Cefalosporines	5	3	10
Miconazole	4	3	0
Fentanyl/Droperidol	5	4	12
Opiates	3	5	2
Benzodiazepines	6	6	2
Dexamethasone	1	0	12
Antihypertensives	0	1	6
Diuretics	4	4	9
Heparine	7	7	2
Dopamine	8	10	3
Dobutamine	6	8	0
Norepinephrine	4	7	0

Table: Medication of critical care patients in whom elimination of metamizol and pentobarbital was studied (n.d.= not determined).

(Novalgin®) clearance and metabolite profile was compared in patients with acute renal failure (creatinine clearance < 30 ml/min/1.73m²) and in those with normal kidney function (see table). After an i.v. metamizol dose of 1.0 - 2.0 g, monomethylaminoantipyrine (MMAAP), aminoantipyrine (AAP), N-acetylaminoantipyrine (AcAAP) and N-formylaminoantipyrine (FAAP) were evaluated by HPLC in plasma and urine.

RESULTS AND DISCUSSION

Fig. 1 shows that pentobarbital clearance is significantly enhanced during the course of treatment, corresponding to increases of D-glucaric acid excretion (2). This inducing effect can be overcome by increasing daily doses of pentobarbital.

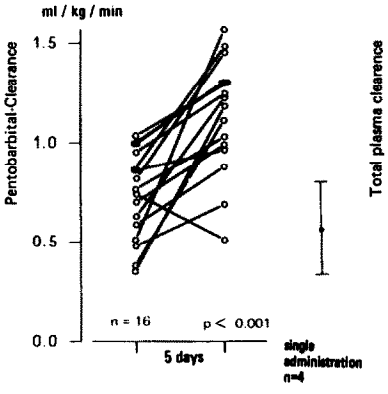

Fig.1 Increase in pentobarbital total plasma clearance during critical care therapy

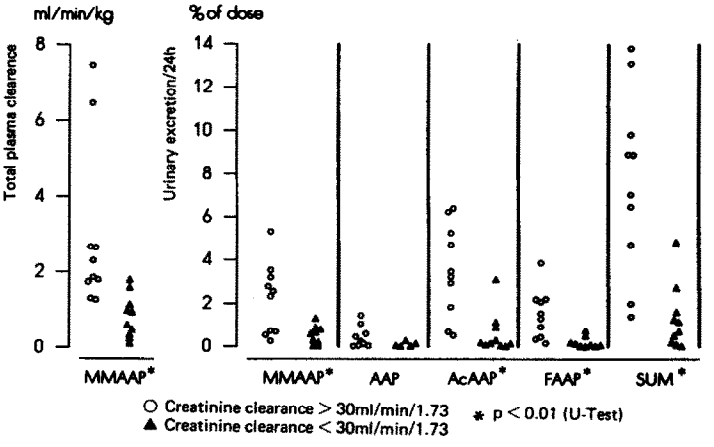

Fig.2 Urinary excretion of MMAAP and its metabolites in 24h-urine in relation to plasma clearance in patients without (o) and with (▲) acute renal failure.

Fig. 2 shows the accumulation of low plasma clearance values of MMAAP in the group of patients with acute renal failure. As MMAAP clearance is mainly accomplished by hepatic metabolism, a direct role of renal insufficiency can be excluded. Earlier experiments in patients with chronic renal failure showed no such impairment (3). Obviously, diminished urinary recovery of metabolites in patients with acute renal failure reflects low rates of hepatic metabolism. Thus, calculation of FAAP invasion constants from plasma data yielded 0.65 ± 0.64 h^{-1} and 0.13 ± 0.096 h^{-1} in patients without and with acute renal failure, resp. As shown in the table, medication was similar in both collectives. Therefore, the observed low clearance values might not be attributable to an interaction with a special drug. Rather, it is assumed that the many drugs given to intensive care patients accumulate (together with respective metabolites) when renal function decreases and thus inhibit the metabolism of metamizol via cytochrome P-450. These unexpected findings suggest that repeated dosages of metamizol should be given with great caution in intensive care patients suffering from acute renal failure. MMAAP half lives may amount to > 20 h instead of 2 - 5 h.

The results show that drug metabolism in critical care patients may be altered in different modes leading to greatly changed pharmacokinetics. Partly such changes can be predicted as they occur in typical situations and patients. However, overdosing or ineffective therapy should be controlled by measuring serum levels.

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