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D-Glucaric acid excretion in critical care patients — comparison with 6β-hydroxycortisol excretion and serum γ-glutamyltranspeptidase activity and relation to multiple drug therapy

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This paper is dedicated to Professor Dr Helmut Kewitz on the occasion of his 65th birthday

1 The incidence of increased drug metabolism activity as a consequence of multiple drug therapy at a surgical intensive care ward has been studied non-invasively by determinations of daily urinary D-glucaric acid (GA) excretion rates.
2 Among 165 randomly selected patients, GA excretion was stimulated in 76 cases (= 46%).
3 Exploratory data analysis showed that increases in GA excretion are primarily due to administration of barbiturates (pentobarbitone, Nembutal®), miconazole (Daktar®) and, to a lesser extent, neuroleptics.
4 Surprisingly, the large number of simultaneously administered additional drugs failed to increase GA excretion.
5 Urinary 6β-hydroxycortisol (6β-OHF) and 17-hydroxycorticosteroid (17-OHCS) excretion rates were correlated in 34 patients with GA excretion; patients not receiving known enzyme inducers showed low GA values but high 6β-OHF and 17-OHCS values, however, with a ratio of 6β-OHF/17-OHCS in the normal range.
6 Patients receiving high dose pentobarbitone treatment failed to exhibit significantly increased 6β-OHF and 17-OHCS or 6β-OHF/17-OHCS values.
7 Miconazole treatment resulted in a significantly increased ratio of 6β-OHF/17-OHCS.
8 γ-Glutamyltranspeptidase activity in serum showed no correlation with GA excretion (n = 91).

Keywords critical care patients D-glucaric acid 6β-hydroxycortisol γ-glutamyltranspeptidase enzyme induction

Introduction

Intensive care patients usually receive a large number of drugs, often with high dosage, placing them at increased risk for drug interactions. Among others, induction of drug metabolism might be an important factor leading to changes in clearance and thereby in the efficiency of certain drugs metabolized oxidatively. Indeed, well-known enzyme inducers such as barbiturates

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are frequently used in critical care patients. On the other hand, the sum of the many drugs given simultaneously may exert an enzyme inducing effect, as well, though the single drug might lack that effect. To date, our knowledge on drugs or drug combinations introducing changes into drug metabolism activity in critical care patients is still incomplete. Considering enzyme induction might aid in optimizing drug therapy, even when pharmacokinetics are altered in such patients in a very complex manner.

For evaluation of enzyme induction, a number of tests are available (Park, 1982), mainly the administration of marker drugs like antipyrine (Vesell *et al.*, 1975), hexobarbitone (Breimer *et al.*, 1978), or aminopyrine (Hildebrandt *et al.*, 1975) and the analysis of their pharmacokinetics. The usefulness of this approach, however, is limited should these test compounds compete with therapeutically given drugs (Vesell, 1979). Therefore, it is not certain that induction is reliably indicated in cases of multiple drug therapy. Moreover, the necessary informed consent is difficult to obtain from an intensive care patient. Thus, non-invasive methods should be preferred.

Determination of the daily urinary excretion rates of D-glucaric acid (GA) and 6β-hydroxycortisol (6β-OHF) are well established non-invasive tools for evaluating drug metabolism activity in man (Hildebrandt *et al.*, 1975; Park, 1982, Roots *et al.*, 1977). GA, as mentioned by Aarts (1965), is a final product of the glucuronic acid pathway. Its formation is stimulated by a number of compounds that can also enhance cytochrome P-450 reactions. Due to this parallelism, GA has been extensively used as an indirect *in vivo* parameter of drug metabolism activity. The literature shows that GA mainly reflects the phenobarbitone type of induction (Cunningham *et al.*, 1974; Davis *et al.*, 1974; Garnham *et al.*, 1970; Hildebrandt *et al.*, 1975; Jackson *et al.*, 1980; Kampf *et al.*, 1980; Perry & Stamp, 1984; Roots *et al.*, 1977). 6β-OHF is formed from cortisol via cytochrome P-450; the amount of this metabolite in a 24 h urine sample has been used to monitor the activity of oxidative drug metabolism (Berman & Green, 1971; Hildebrandt *et al.*, 1975; Ohnhaus & Park, 1979; Roots *et al.*, 1979). The extent of 6β-OHF formation, however, also depends on the daily cortisol formation whose variation is compensated for by referring 6β-OHF values to excretion rates of 17-hydroxycorticosteroids (17-OHCS). As a further parameter for examining enzyme inducing effects, the activity of serum γ-glutamyl transpeptidase (γ-GT) has been described (Hildebrandt *et al.*, 1975; Rosalki *et al.*, 1971; Whitfield *et al.*, 1973).

The aim of the present study was to detect those patients at a surgical intensive care ward in whom increased GA excretion is present, possibly indicating enzyme induction. Moreover, it was attempted to find out what drugs or drug combinations are associated with increased values of GA. The study was designed as a screening of GA excretion in randomly selected patients to provide an unbiased primary survey of almost all stages of treatment and disease. In part of that collective, 6β-OHF and γ-GT were measured as well.

Methods

Patients

The study included 165 patients (103 male and 62 female, American Surgical Association (ASA) classification III and IV), ranging in age from 6–75 years, from the surgical intensive care units of the 'Klinikum Steglitz' (n = 145) and 'Krankenhaus am Urban' (n = 20), Berlin. The diagnoses are given in Table 1. Table 2 shows the number of these patients with regard to the period of hospitalization at the intensive care unit. For comparison, numbers of all intensive care patients treated during the year of this study are included. Patients staying 1–2 days are underrepresented here as they were mostly classified according to ASA II. From all patients staying longer than 2 days those studied for GA (n = 147) represented 40% of all patients treated during 1 year (Table 2).

The screening was performed by determinations of GA in all of these randomly selected

Table 1 Diagnoses of 165 intensive care patients randomly selected for evaluation of urinary D-glucaric acid excretion rates

Diagnosis	n	%
Intracranial haemorrhage	27	16.4
Intracranial tumours	16	9.7
Severe head injury	20	12.1
Polytrauma	16	9.7
Abdominal tumours	28	17.0
Peritonitis	8	4.8
Arterioplasty	9	5.5
Other abdominal diseases	23	14.0
Neck dissection	4	2.4
Burns	2	1.2
Other	12	7.2
	165	100.0

Table 2 Number of intensive care patients evaluated for daily urinary D-glucaric acid excretion in correlation with the length of their stay at the intensive care unit and in comparison to all surgical intensive care patients treated during the year of the study.

Length of stay (days)	*1–2*	*3–5*	*6–8*	*9–12*	*13–15*	*16–20*	*21–30*	*> 30*	*sum*
				All intensive care patients treated in the year of study					
n	371	149	62	48	18	21	48	41	758
%	49	21	8	6	2	3	6	5	100
				Intensive care patients randomly selected					
n	18	39	37	17	10	18	16	10	165
%	11	24	22	10	6	11	10	6	100

patients. Patients with acute renal failure and those who had received known inducing agents up to 5 days previously, excepting the day on which the study was carried out, were excluded. A few patients were studied at different times and stages of intensive care treatment. 6β-OHF was determined in 34 and γ-GT activity in 91 patients. Drugs prescribed for continuous medication were recorded, as well as the period of their administration. Drugs given by single doses were not considered.

Methodology

GA was measured by a modification (Hildebrandt *et al.*, 1975) of the method of Marsh (1963) with further modifications: In a triplicate assay, 0.1–0.5 ml of the urine (acid or alkali treated) was preincubated for 20 min together with β-glucuronidase/arylsulphatase from *Helix pomatia* (Boehringer, Mannheim) 0.006 mU ml^{-1} at pH 4.5 in acetate buffer (0.1 mol l^{-1}). The reaction was started with *p*-nitrophenyl-glucuronide (0.94 mmol l^{-1}). Incubation was stopped after 20 min by the addition of 4 ml of 0.15 N NaOH. *p*-Nitrophenol was determined at 405 nm in a Gilford N 300 or a Kontron Uvikon 810 spectrophotometer, both equipped with sipper cuvettes. The coefficient of variation (CV) for a control urine was 7.2% for the overall procedure (n = 12); CV was 6.0% for the acid treated and 6.2% for the alkali treated fraction. 6β-Hydroxycortisol (6β-OHF) was measured by high pressure liquid chromatography as described by Roots *et al.* (1979). 17-OHCS were measured according to Sanghvi *et al.* (1973). The activity of serum γ-GT was determined using a standard test kit (Boehringer, Mannheim).

Statistics

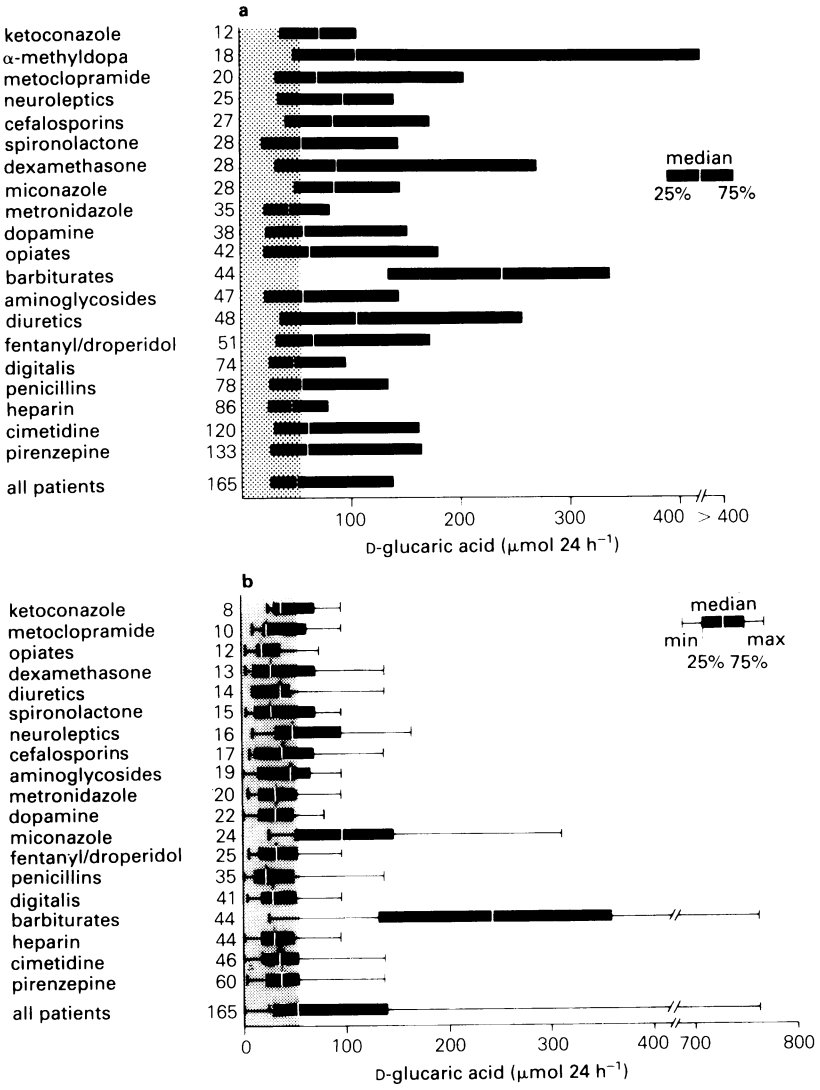
Exploratory data analysis (Tukey, 1972) was applied to evaluate changes in GA excretion as influenced by the different drugs. This evaluation is performed by the use of 'box-and-whisker-plots', giving minimum, 25 %-quantile, median, 75%-quantile and maximum of GA in connection with each drug. Data handling is as follows: Patients of the drug group showing the highest GA excretion are subtracted from the whole collective. Thus, a potential stimulator of GA excretion is eliminated from other drug groups. The remainder is then subjected repeatedly to the same procedure. Finally, all drug collectives are devoid of patients co-medicated with other drugs that stimulate GA excretion. The mean values of these groups were then statistically evaluated by multiple analysis of variance (Duncan-test). Correlation between GA and γ-GT was calculated by the χ^2-test. Differences in GA excretion during pentobarbitone or miconazole administration were examined by the *t*-test. 6β-OHF and 17-OHCS excretion in different groups of patients were compared by the U-test.

Results

Drug administration and excretion of D-glucaric acid

Figure 1a, b contains the main drugs which were administered continuously to at least 7% of the patients, arranged according to frequency of use. The following groups comprise several agents: *penicillins:* penicillin G, flucloxacillin, azlocillin, mezlocillin; *aminoglycosides:* tobramycin, netilmycin, amikacin; *neuroleptics:* chlorprothixene, haloperidol, chlorpromazine; *opiates:* fentanyl, meperidine, piritramide, pentazocine; *barbiturates:* pentobarbitone, phenobarbitone, thiopentone, some antiepileptics (phenytoin, primidone); *cefalosporins:* cefotaxim, cefazolin; *digitalis:* digoxin, digitoxin; *diuretics:* frusemide, mefruside. Mechanically ventilated patients were given a standard analgesic and sedative combination of fentanyl and droperidol noted separately.

Figure 1a shows urinary GA excretion in 165



Figures 1 a and b Daily urinary excretion of D-glucaric acid (GA) in 165 intensive care patients with reference to drug treatment.
Figure 1a gives median as well as 25%- and 75%-quantile for GA-values in connection with each drug prescribed as continuous medication. Drugs administered to less than 7% of all patients are not considered. Figure 1b shows minimum 25%-quantile, median, 75%-quantile and maximum for GA-excretion after application of exploratory data analysis according to Tukey (1972). By this procedure, patients receiving barbiturates, miconazole or neuroleptics were subtracted from the whole collective. The normal range is given by the hatched area.

randomly selected patients before drug collectives were refined by exploratory data analysis. The bars represent 25 %-quantile, median and 75 %-quantile; minimum and maximum values are omitted as they are alike for all groups, ranging from close to zero to 763 μmol 24 h^{-1}. For comparison, the normal range as found in the healthy is given by the hatched area, representing the mean value (30 μmol 24 h^{-1}) plus two standard deviations (Hildebrandt *et al.*, 1975). Altogether, 76 patients (= 46%) show GA values exceeding this upper normal limit of 55 μmol 24 h^{-1}.

As expected, barbiturate treatment is associated with the greatest enhancement of GA

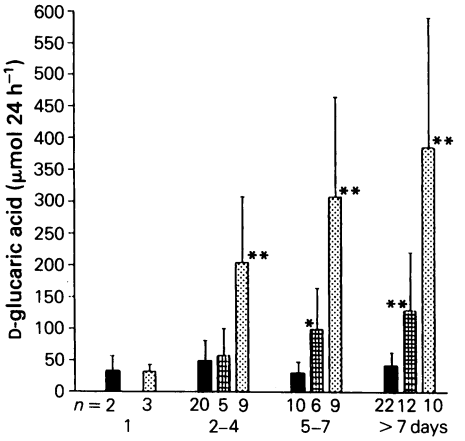


Figure 2 Increase of daily urinary excretion of D-glucaric acid in critical care patients according to duration of pentobarbitone (▨) or miconazole (■) administration as compared to patients without such medication (■). (Mean ± s.d., * $P < 0.01$, ** $P < 0.001$).

excretion. Primarily, pentobarbitone (Nembutal®) was used, in a dose of 30 mg kg^{-1} day^{-1} to reduce increased intracranial pressure in patients with severe head injury or intracranial haemorrhage. High values of GA excretion were found for most of the other drugs listed as well. A causal relationship, however, cannot be deduced directly, as the average patient received simultaneously six of the drugs listed. Applying exploratory data analysis, all patients receiving barbiturates were excluded from the whole collective. The remainder was evaluated for other drugs associated with increased GA excretion. The final result, after repeating the procedure twice, is depicted in Figure 1b by complete 'box-and-whisker-plots'. The drug groups found to be associated with increased GA excretion, obviously differed in their potency. Barbiturates were the most potent stimulators in these patients with a minimum, 25 %-quantile, median, 75 %-quantile and a maximum of 25, 132, 243, 359 and 763 μmol 24 h^{-1}, respectively. Figure 1b comprises all drugs that were given to at least 10% of all patients after subtracting drugs increasing GA. Thus, e.g. α-methyldopa does not appear, as almost all of the 18 patients shown in Figure 1a received barbiturates as well.

Next to barbiturates, miconazole (Daktar®) led to increased GA values with minimum, 25%-quantile, median, 75%-quantile and maximum of 24, 50, 96, 147 and 312 μmol 24 h^{-1}, respectively. Miconazole was given in doses of 1 g day^{-1} to treat systemic fungal infections occurring after broad spectrum antibiotic treatment. A slight increase in GA excretion seems to be associated with neuroleptic agents. Sixteen patients received haloperidol, chlorprothixene or chlorpromazine, but no barbiturates or miconazole. The daily excretion of GA was 9, 31, 49, 96 and 166 μmol 24 h^{-1} (minimum, 25%-quantile, median, 75%-quantile and maximum, respectively).

Multiple analysis of variance revealed statistical significance for the difference of mean GA excretion between the barbiturate group and all others ($P < 0.001$) as well as between miconazole and the remainder ($P < 0.01$). No statistical significance was found for the other groups. Nevertheless, patients treated with neuroleptics remained separated in Figure 1b in order to demonstrate the effect of the other drugs as clearly as possible. Among the 81 patients who had not received barbiturates, miconazole or neuroleptics, 11 (= 6.6% of all patients) exhibited increased values.

Time course of D-glucaric acid excretion during pentobarbitone and miconazole treatment

In Figure 2 GA excretion values are arranged according to the duration of treatment with pentobarbitone or miconazole. A seven-fold increase of GA excretion occurs already on days 2–4 of pentobarbitone administration which is usually given during the first 10 days following admission to the intensive care unit. Miconazole was given mostly during later stages of treatment; GA excretion showed a slower onset. A significant increase was evident after 5–7 days (88 ± 98 μmol 24 h^{-1}) and a further increase reached 125 ± 98 μmol 24 h^{-1} after more than 7 days.

Excretion of 6β-hydroxycortisol and 17-hydroxycorticosteroids

To test the notion of increased GA as an indication of enzyme induction and to detect possible additional effects, 6β-OHF and 17-OHCS were measured (Table 3). In order to elucidate clearly effects of pentobarbitone and miconazole, random selection of patients was not performed. Instead, all patients had received these drugs for at least 5 days, a period long enough to increase significantly GA excretion. As 6β-OHF formation is known to be influenced by glucocorticoids, all patients receiving such drugs were excluded. Patients with barbiturate or miconazole treatment were therefore compared to those who neither received these drugs nor glucocorticoids and showed GA excretion to be within the normal range.

Table 3 Excretion of 6β-hydroxycortisol as related to 17-hydroxy-corticosteroids and D-glucaric acid in critical care patients.

	D-glucaric acid ($\mu mol\ 24\ h^{-1}$)	*6β-OHF* ($\mu g\ 24\ h^{-1}$)	*17-OHCS* ($\mu g\ 24\ h^{-1}$)	*6β-OHF/17-OHCS*
Group A	37	400	27600	0.014
no barbiturates,	31	40	1400	0.029
no miconazole	50	1110	55900	0.020
(n = 17)	23	730	15890	0.046
	17	430	15130	0.028
	10	200	13700	0.015
	30	3930	63170	0.062
	16	440	77900	0.006
	25	1820	23750	0.077
	49	2910	24960	0.117
	45	2480	40690	0.061
	19	150	13890	0.011
	58	310	42000	0.007
	11	2960	29780	0.099
	29	1975	8180	0.241
	49	2920	62790	0.047
	4	225	16990	0.013
Mean	31.5	1412	33760	0.051
s.d.	17.7	1258	23710	0.057
median	29.0	730	24960	0.029
Group B	111	1230	63800	0.019
barbiturate	768	748	32770	0.023
(n = 6)	n.d.	624	12180	0.051
	200	1130	51170	0.022
	285	1245	15450	0.081
	300	2775	91000	0.031
Mean	334	1292	44390	0.038
s.d.	255	771	30340	0.024
Median	285	1180	41970	0.027
P (*vs* A)	< 0.001	NS	NS	NS
Group C	71	4290	5760	0.745
miconazole	66	183	7870	0.023
(n = 11)	n.d.	2350	18350	0.128
	228	5550	22150	0.251
	106	480	48270	0.010
	98	1250	17650	0.071
	31	870	13610	0.064
	147	1140	12050	0.095
	24	2570	32700	0.079
	56	1370	17250	0.079
	41	1630	27270	0.060
Mean	86.8	1971	20260	0.145
s.d.	62.2	1643	12190	0.209
Median	68.5	1370	17650	0.079
P (*vs* A)	< 0.01	NS	NS	< 0.05

n.d. not determined

In group A, 6β-OHF excretion varied from 40 up to 3930 $\mu g\ 24\ h^{-1}$, with 11 out of 17 patients exceeding the upper normal limit of 423 $\mu g\ 24\ h^{-1}$ (mean ± 2 s.d.) (Roots *et al.*, 1979). These high values are paralleled by high 17-OHCS excretion rates, except for two patients. Thus, the median of the ratio of 6β-OHF/17-OHCS is within the normal range found for healthy volunteers. Regarding 6β-OHF excretion, administration of barbiturates (group B) surprisingly yielded no statistical difference as compared to group A. Values ranged from 624 to 2775 $\mu g\ 24\ h^{-1}$, and 17-OHCS excretion was also increased. In patients receiving miconazole

(group C), the ratio of 6β-OHF/17-OHCS was significantly increased 3-fold as compared to the control group A.

D-glucaric acid excretion and activity of serum γ-GT

The activity of serum γ-GT was correlated with the excretion rate of GA in 91 randomly selected intensive care patients (Figure 3). To discriminate the specific effect of drug treatment on γ-GT activity from an increase due to liver damage, GOT and GPT values were also determined. Upper limits in men and women reached up to 23 and 18 u l^{-1} for GPT and 19 and 15 u l^{-1} for GOT, respectively. A correlation was lacking among patients with pathological values ($n = 66$) and also in patients with normal transaminases ($n = 25$).

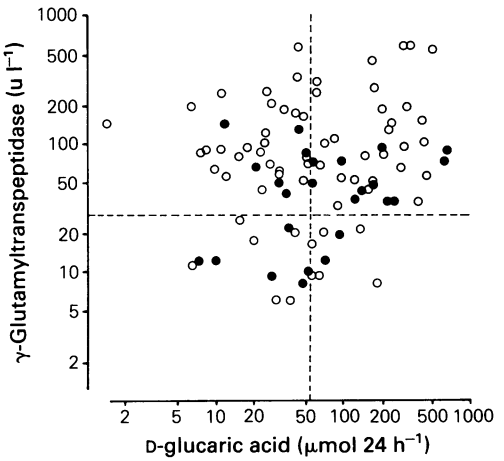


Figure 3 Relation between daily D-glucaric acid excretion and activity of serum γ-glutamyltranspeptidase in 91 patients with normal (●) or increased (○) transaminases. The upper normal limits are given by the dashed lines.

Discussion

This primarily epidemiologically orientated investigation is an attempt to evaluate the occurrence of enzyme induction in a surgical intensive care ward. Major aims were to estimate the incidence of induced patients and to recognize drugs or drug combinations with inducing potency. Initial ideas date back to the study of Sotaniemi *et al.* (1974) who correlated GA excretion in randomly selected patients with respective number and kind of drugs. Well aware of the limitations of all the three non-invasive approaches (GA, 6β-OHF and γ-GT) (Park, 1982; Roots *et al.*, 1977), this study was focused on GA due to the ease of its routine determination and since the least interferences with drugs, typically given in very high number, were expected.

Excretion pattern of D-glucaric acid

Numerous animal experiments and clinical pharmacological studies demonstrated that the effect of several enzyme inducers is reliably indicated by strongly increased GA excretion (Hildebrandt *et al.*, 1975; Davis *et al.*, 1974; Cunningham *et al.*, 1974; Jackson *et al.*, 1980; Mezey, 1976). Excellent correlation between GA excretion and antipyrine clearance has been presented recently in a collective of epileptics by Perucca *et al.* (1984). Hardly a foreign compound is known that results in increased GA excretion which is not accompanied by an enhancement of one or the other cytochrome P-450 reaction. By virtue of a parallel effect on enzyme activities of the glucuronic acid pathway and on the cytochrome P-450 system, GA can be used as an indirect parameter of changes in cytochrome P-450 activity. The disadvantage of GA having no direct connection with cytochrome P-450, may turn out an advantage: potentially misleading results due to competition with the numerous drugs given during intensive care therapy may be avoided. In non-induced humans either no correlation exists between GA excretion and drug kinetics (Cunningham *et al.*, 1974; Smith & Rawlins, 1974) or only a weak one (Hildebrandt *et al.*, 1975). This seems understandable, as separately controlled metabolic steps are involved.

Figure 1a shows that about half the patients have clearly increased GA values pointing to the possible presence of enzyme induction. Exploratory data analysis revealed that only barbiturates, miconazole and possibly neuroleptics are responsible for these major changes in GA excretion. None of the patients suffered from renal insufficiency. No effect of artificial ventilation or parenteral nutrition was observed.

The expected stimulating effect of *pentobarbitone* (Figure 2) on GA excretion was paralleled by a significant increase in pentobarbitone plasma clearance within 5 days from 0.73 up to 1.34 ml min^{-1} kg^{-1} (Heinemeyer *et al.*, 1985a). The rapid rise in GA excretion within a few days corresponds to the exceptionally high pentobarbitone doses of about 2 g day^{-1}.

Miconazole was also identified as an important stimulator of GA excretion. This novel association becomes even clearer when duration of

miconazole treatment is considered (Figure 2). Moreover, a separate study showed an intra-individual rise in GA excretion in patients studied before and after 8 days of miconazole administration (Heinemeyer & Jaeck, 1983). Further experiments with patients should clarify whether this reflects increases in cytochrome P-450 activity as well. Miconazole and other imidazole derivatives have already been shown as potent inducers in animal studies (Christ *et al.*, 1980; Niemeegers *et al.*, 1981). On the other hand, inhibition of drug metabolism by these compounds *in vivo* and in *vitro* has been well known (Heinemeyer *et al.*, 1985b; Niemeegers *et al.*, 1981).

The finding that *neuroleptics* are associated with slightly increased GA values conforms with results from Wright *et al.* (1984) who detected such an effect in patients receiving chlorpromazine or fluphenazine.

6β-*Hydroxycortisol*

Since GA excretion represents only an indirect parameter of drug metabolism activity, it was of interest to measure 6β-OHF, which is formed via hepatic cytochrome P-450 and therefore might directly indicate enzyme induction. Specificity of some inducers differs towards 6β-OHF and GA. Thus, rifampicin (Ohnhaus & Park, 1979; Roots, 1979; Yamada & Iwai, 1976) only slightly enhances GA-excretion, but leads to an about 10-fold increase in 6β-OHF. Both parameters are unable to indicate methylcholanthrene type of induction (Roots *et al.*, 1977) e.g. by tobacco smoking.

In 11 out of 17 critical care patients not receiving known inducers (Table 3), 6β-OHF excretion exceeded upper normal limits (426 μg day^{-1}, mean + 2 s.d., Roots *et al.*, 1979), partly paralleled by increased 17-OHCS. In some of these patients, urinary excretion of free cortisol was also increased (unpublished data). This might be due to increased cortisol production as a result of stress (Finlay & McKee, 1982). Further, Frantz *et al.* (1960) and Werk *et al.* (1964) reported that in terminal illness and toxaemia 6β-OHF excretion is increased. Interestingly, the ratio of 6β-OHF/17-OHCS in the collective not receiving known enzyme inducers was elevated in few cases only, indicating agreement with GA-values.

The question, however, whether 6β-OHF or the ratio of 6β-OHF/17-OHCS can definitely indicate the effects of known inducers in critical care patients, remains open: Six patients subjected to high dose *pentobarbitone* therapy (Table 3) exhibiting 6β-OHF values exceeding the upper normal limit did not differ from the patients without administration of known inducers. The 17-OHCS fraction was extremely high (presumably due to extreme stress) and led to as low values in the ratio of 6β-OHF/17-OHCS as found in healthy control persons. The failure to indicate enzyme induction in these patients might reside in a competition of inducer and marker substrate (i.e. cortisol) at the cytochrome P-450 level. Such a basically well known effect might mask the well-documented increases in 6β-OHF/17-OHCS upon barbiturate administration.

The significant elevation of 6β-OHF/17-OHCS by *miconazole* conforms with increased GA values in this collective (Table 3) and may corroborate the discussed enzyme inducing property. As already mentioned, miconazole is a potent inhibitor of cytochrome P-450 reactions (Niemeegers *et al.*, 1981), as demonstrated by us in critical care patients by a strongly inhibited pentobarbitone elimination (Heinemeyer *et al.*, 1985b). Moreover, imidazole-antimycotics inhibit formation of endogeneous substances such as testosterone and cortisol (Schürmeyer & Nieschlag, 1984). The complexity of interactions introduced by miconazole cannot be resolved by the present data and should be studied separately.

γ-*Glutamyltranspeptidase*

Similarly as GA, increased γ-GT values only indirectly point to induction of the cytochrome P-450 system. Moreover, liver damage etc. may unspecifically increase this parameter. Figure 3 shows many patients with high values of transaminases, indicating that intensive care treatment may lead to liver damage, for instance by parenteral nutrition (Lindor *et al.*, 1979). Thus, increases in γ-GT during the course of intensive care treatment as reported by Rietbrock *et al.* (1979, 1981), do not necessarily reflect enzyme induction.

Concluding remarks

As long as a better parameter is missing, GA seems acceptable in screening for increased drug metabolism activity among intensive care patients. Parallel determinations of 6β-OHF and 17-OHCS may corroborate any conclusions. On principle, unspecific influences on GA excretion rates, such as major changes in diet, presence of certain diseases, enzyme inhibition by certain drugs etc. may result in false interpretations. However, this study design offered no hint for such a situation. Thus, the group of

patients that did not receive known enzyme inducing compounds exhibits an almost normal pattern of GA excretion. The validity of GA measurements presented here should be controlled by an intraindividual longitudinal evaluation.

Are increased GA excretion rates indeed paralleled by increased clearance of drugs given to intensive care patients? We have recently shown that pentobarbitone clearance was significantly elevated (Heinemeyer *et al.*, 1985a) in parallel to GA excretion (cf. Figure 2). A similar effect was found for hexobarbitone but not with metamizol (Heinemeyer *et al.*, 1984). Thus, a straightforward association between drug metabolism activity and GA values cannot always be expected, since other factors such as competitive inhibition (Heinemeyer *et al.*, 1985 a, b), changes in plasma protein binding or deranged liver, kidney or circulatory function also might play an important role in altering pharmacokinetics.

Considering this complexity, it is conceivable that increased GA values do not automatically indicate the necessity for a higher drug dose. GA is just one parameter to elucidate drug interactions which should be studied separately for all important drug combinations by pharmacokinetic means. Patients with various diseases and stages thereof have to be implicated. Nevertheless, this study demonstrated the routine applicability of GA as *in vivo* parameter of drug metabolizing enzyme activity in patients receiving multiple drug therapy. The epidemiologic approach allowed to discriminate those few drugs that led to increased GA excretion in about half the collective from the majority of drugs that are devoid of this effect.

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