factor of 4–10, despite similar plasma concentrations. As canrenone is extensively bound (> 89%) to plasma proteins (Karim, Zagarella, Hribar & Dooley, 1976) we suggest that in the steady state situation, major metabolic pathways of canrenone (Ochs *et al.*, 1978) become saturated at around a daily dosage of 300 mg of spironolactone. The extra 100 mg per day of spironolactone with a consequent increase in canrenone production may result directly in increased urinary canrenone excretion, without any marked change in the plasma concentrations.

The incidence of side-effects during the trial period was high (85%) in contrast to other trials using a 100 mg daily dose of spironolactone (Hennigsen, 1978; Ludbrook *et al.*, 1980; Madwar, 1980). Our data did not indicate that either divided or single dose spironolactone reduce the incidence of side-effects. Previous studies have shown these effects to be dose-

related (Ogilvie, Piafsky & Ruedy, 1978). High daily dose spironolactone can provide effective 24 h blood pressure control but the side-effects may make these larger doses unacceptable in some patients.

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THE EFFECT OF NITRAZEPAM AND OTHER HYPNOTICS ON PLATELET 5-HT UPTAKE

There have been several reports of a reduction in the rate of uptake of 5-hydroxytryptamine (5-HT) by blood platelets from depressed patients (Tuomisto & Tukiainen, 1976; Tuomisto, Tukiainen & Ahlfors, 1979; Coppen, Swade & Wood, 1978; Dreux, Lounay & Giret, 1979; Scott, Reading & Loudon, 1979).

Many patients with affective disorders suffer from sleep disturbances and consequently require or demand hypnotic drugs. It therefore seemed appropriate to investigate the effect of nitrazepam and other hypnotics on platelet 5-HT uptake in depressive patients and control subjects.

Table 1 Characteristics of 5-HT uptake by platelets from control subjects and depressed patients and the effect of hypnotics (mean $\pm$ s.e. mean)

Treatment group	n	Age (years)	HRS	K_m (μ M)	V_{max} (pmol/ 10^8 platelets/min)
Control subjects	28	45.1 $\pm$ 1.9	—	0.45 $\pm$ 0.02	46.5 $\pm$ 3.4
Drug-free patients	13	43.4 $\pm$ 3.8	17.6 $\pm$ 1.3	0.50 $\pm$ 0.06	34.8 ³ $\pm$ 2.7
Nitrazepam	18	55.2 ¹ $\pm$ 2.4	19.3 $\pm$ 0.8	0.57 $\pm$ 0.06	22.4 ⁴ $\pm$ 2.4
Triazolam	6	62.3 ¹ $\pm$ 3.5	19.7 $\pm$ 2.5	0.47 $\pm$ 0.08	32.8 $\pm$ 5.0
Chloral hydrate	5	53.8 $\pm$ 7.8	25.2 ² $\pm$ 1.6	0.50 $\pm$ 0.16	31.9 ³ $\pm$ 3.9

¹ Older than control subjects and drug-free patients $P < 0.01$ ² More depressed than both drug-free patients and nitrazepam group $P < 0.02$.³ Lower than control subjects $P < 0.02$ ⁴ Lower than control subjects $P < 0.001$, and lower than drug-free patients $P < 0.01$.

The patients suffered from depressive illness (MRC, 1965), and had no history of mania and no significant physical illness. All patients were withdrawn from any antidepressant or neuroleptic medication for 7 to 10 days before the determination of blood platelet 5-HT uptake characteristics. At the end of this period the patients were assessed for the severity of their symptoms by the Hamilton Rating Scale (HRS) (Hamilton, 1967). Only those patients who scored 12 or more on the first 16 items of the scale were included in this study.

Many of the patients were receiving hypnotics prescribed by their general practitioner. Four groups of depressed patients were studied; 13 patients had not received any hypnotic medication for at least 7 days; 18 patients were receiving nitrazepam (5 or 10 mg); 6 patients were receiving triazolam (0.25 or 0.50 mg); and 5 patients were receiving chloral hydrate (500 mg or 1 g). A group of 28 normal control subjects were studied. All the controls were physically well and completely free of any medication at the time of the test, and none had a history of psychiatric illness.

Seven control subjects were tested when drug-free. They then took 10 mg of nitrazepam at 22.00 h for 4 nights. The subjects were retested on the morning following the last dose, and again 4 days later.

The method of determination of platelet 5-HT uptake characteristics was the same for all subjects studied, and was similar to that described previously (Coppin *et al.*, 1978).

As reported previously, V_{max} of 5-HT uptake by platelets was found to be significantly lower in drug-free depressed patients than in control subjects (Table 1). Depressed patients who were taking nitrazepam had significantly lower values of V_{max} than both drug-free depressed patients and control subjects. In patients taking either triazolam or chloral hydrate the value of V_{max} was lower than that obtained for control subjects, but was not significantly different from that obtained for drug-free patients. Patients who were receiving hypnotics were older than those who were drug-free but there was no significant correlation between age and platelet 5-HT characteristics in any of the subject groups.

There was no significant difference in severity of morbidity between the drug-free patients and those on nitrazepam or triazolam. The patients on chloral hydrate were significantly more depressed than both the drug-free and nitrazepam groups. In the patients receiving nitrazepam there was a significant correlation between HRS and V_{max} ($r = -0.51$, $P < 0.05$), but a similar correlation was not found in the other groups. It is unlikely, therefore, that differences in morbidity would account for the observed differences in platelet 5-HT uptake.

We have previously reported that lithium therapy increases the value of V_{max} of depressive patients to normal (Coppin, Swade & Wood, 1980). However, when nitrazepam is taken in conjunction with lithium, the value of V_{max} is significantly lower than in

Table 2 Characteristics of 5-HT uptake by platelets from patients treated with lithium alone or with lithium and nitrazepam (mean $\pm$ s.e. mean)

Group	n	Age (years)	K_m (μ M)	V_{max} (pmol/ 10^8 platelets/min)	Lithium level (mmol/l)
Patients on lithium only	21	55.6 $\pm$ 2.6	0.50 $\pm$ 0.03	42.7 $\pm$ 4.0	0.85 $\pm$ 0.04
Patients on lithium + nitrazepam	21	61.8 $\pm$ 1.9	0.49 $\pm$ 0.03	28.2 ¹ $\pm$ 2.7	0.95 $\pm$ 0.04

¹ Lower than patients on lithium only $P < 0.01$.

Table 3 The effect of nitrazepam on 5-HT uptake by platelets from control subjects (mean $\pm$ s.e. mean)

Group	n	K_m (μM)	V_{max} (pmol/ 10^8 platelets/min)
Control subjects	7	0.41 ± 0.03	39.9 ± 6.3
Controls on nitrazepam	7	$0.31^1 \pm 0.02$	$31.3^2 \pm 5.7$
4 days after discontinuation	6	0.40 ± 0.03	$31.0^3 \pm 7.4$

¹ Lower than baseline $P < 0.05$, lower than after discontinuation $P < 0.01$ ² Lower than baseline $P < 0.055$ ³ Lower than baseline $P < 0.02$

patients on lithium only (Table 2). There was no significant difference between these groups of patients in age, plasma lithium concentration at time of test, or affective morbidity index.

Healthy control subjects showed a 22% reduction in both V_{max} and K_m after taking nitrazepam at night for 4 nights (Table 3). After 4 drug-free days the value of K_m was restored to normal, but V_{max} was still significantly lower than the drug-free baseline value.

In biochemical investigations of depressive illness it is often assumed that the benzodiazepines have little effect on amine metabolism and transport. This study has shown in the case of nitrazepam that this is not so. We have found that depressive patients treated with nitrazepam have a significantly lower rate of platelet 5-HT uptake than patients not treated with hypnotics, or patients treated with triazolam or chloral hydrate. Nitrazepam also reduces the rate of platelet 5-HT uptake in patients receiving lithium. We also found a similar effect which persisted for at least 4 days after discontinuation in control subjects. This is probably related to the long half-life of nitrazepam (21 to 28 h; Rieder & Wendt, 1973). Triazolam, a

benzodiazepine with a half-life of only 2 h (Eberts, Philopoulos & Vliek, 1979), does not appear to affect platelet 5-HT uptake.

Depressed patients have a reduced rate of platelet 5-HT uptake, and nitrazepam increases the extent of this abnormality. This increase in abnormality is not reflected in the depressive morbidity in either depressed patients or in patients on long-term lithium therapy.

In conclusion, this study has shown the importance of investigating the action of commonly administered drugs on the biochemical variates being studied in investigations of depressive illness. Depressive patients are frequently given hypnotics and anxiolytics, and the actions of these drugs should be elucidated before it is concluded that they have no effect on any particular biochemical test.

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