1.63 ± 0.43 mmol) and Mg^{++} (0.70 ± 0.50 , 0.84 ± 0.34 mmol) obtained after administration of Impugan and Lasix respectively.

Comparisons between the bioavailability of synonymous drug preparations can be based on plasma levels and urinary recovery of the drug or on effects of the compounds in single or multiple dose regimens.

Chronic treatment of healthy volunteers with frusemide would be rather inconvenient to the subjects. Thus we chose a single-dose design with measurement of several pharmacokinetic and pharmacodynamic parameters.

The time of the peak levels of frusemide did not differ significantly between Impugan and Lasix. The similarities in the area under plasma concentration time curves and in the urinary recovery after oral administration of Impugan and Lasix indicate that the two preparations do not differ in bioavailability.

When comparing the bioavailability of a compound with pharmacodynamic parameters, it is essential that the dose given is on the steep part of the dose response curve. This prerequisite is fulfilled for a 40 mg dose of frusemide (Kleinfelder, 1963). Thus the similarity in the diuretic response and in the increase in electrolyte excretion after 40 mg frusemide as Impugan and Lasix strongly supports the view that the two brands of frusemide are generically equivalent.

The skilful technical assistance of Miss Susanne Floberg is acknowledged. The study was financially supported by the Swedish Medical Research Council

(Grant No B 77-19 $\times$ -00227-13) and Dumex AB, Helsingborg, Sweden.

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Received October 4, 1977

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PLATELET AGGREGATION AND CHLORPROMAZINE THERAPY

Recently we have attempted to replicate earlier data showing enhancement of 5-HT induced aggregation of platelets from patients taking chlorpromazine (CPZ). Twenty-two tests have been made in fourteen patients and in only one case has enhancement been observed. In this recent study the patients came from another mental hospital, but as far as we are aware there are no methodological problems which could account for the failure to repeat the earlier observations. Enhancement is still being observed in some of the patients involved in the original study of 1974/5 (Boullin, Woods, Grimes, Grahame-Smith, Wiles, Gelder, & Kolakowska, 1975; Boullin & Grimes, 1976).

Table 1 compares the recent observations with those of the 1974/5 study. It is quite clear that 5-HT aggregation responses are normal. On the other hand

Table 2 shows that plasma CPZ was quite high in eight of the fourteen subjects studied now; plasma CPZ was measured in only three subjects in the original investigation.

At an international meeting concerned with the pharmacology of platelets, held in Florence in September, 1977, Boullin, Orr & Peters reported that 25 out of 34 patients showed enhancement of 5-HT induced aggregation. They suggested the phenomenon might have value as a predictive test for treatment of schizophrenics. The proceedings of the meeting in which those views were expressed are in press (Boullin, Orr & Peters, 1978). Accordingly it is necessary for us to publish the new results and to state that the views expressed earlier will need re-evaluation. Although platelet aggregation responses to 5-HT may have some predictive value in the CPZ treatment of

schizophrenia, this cannot be established until the explanation for the failure to replicate the earlier results has been discovered.

There are a number of possibilities:

1. *Differences in patient population* This is a likely explanation since the group studied in 1978 appear to be somewhat different from those seen in 1974/5. These may have had a higher stress level than the 1978 group. Ball, Boullin & Glenton (1977) and Boullin & Glenton (1978) have reported that noradrenaline enhances 5-HT induced aggregation: this enhancement can produce 5-HT aggregation responses indistinguishable from those seen with CPZ treated patients (Boullin *et al.*, 1975). Thus it is possible that 5-HT enhancement is due to high plasma catecholamines and that these occur in stressed

schizophrenics treated with CPZ. We have not yet made such measurements in our patients, but Benedict & Grahame-Smith (1978) have reported plasma noradrenaline concentrations up to 4 ng/ml (23 pmol/ml) in patients with septicaemia and haemorrhagic shock, though these patients were grossly stressed.

Ball, Boullin & Glenton (1977) enhanced 5-HT aggregation with 100 pmol/ml noradrenaline, and Boullin (unpublished observations) finds that 10 pmol/ml is also effective. Accordingly there is some factual basis for the potential involvement of plasma noradrenaline in platelet 5-HT induced aggregation.

2. *Metabolic adaptation* The patients forming the 1978 study have been hospitalized for many years and received CPZ for a minimum of 2 years. It is possible

Table 1 Platelet aggregation responses in chronic schizophrenics treated with CPZ

Year	1974/5	1974/5	1978 (1)	1978 (2)
	<i>Initial rate of aggregation</i> (V_{max} μ V/min)			
	<i>Controls</i> n=13	<i>CPZ</i> n=9	<i>CPZ</i> n=13	<i>CPZ</i> n=9
5-HT	771 $\pm$ 192	1819 $\pm$ 246	393 $\pm$ 74	1285 $\pm$ 170
ADP	3415 $\pm$ 323	3451 $\pm$ 347	1325 $\pm$ 215	4198 $\pm$ 387
5-HT as % ADP	22.6	52.8	30.3	31.4

Platelet aggregation was measured as described earlier (Boullin *et al.*, 1975; Boullin & Grimes, 1976).

Each set of data refer to separate groups of subjects tested at the dates indicated. In the case of those examined in 1978 the subjects were examined several weeks apart and are therefore enumerated in 2 groups (1 and 2). The data relating to Group 2 are given in greater detail in Table 2.

Table 2 5-HT aggregation and plasma CPZ in eight schizophrenic patients

<i>Patient number</i>	<i>Plasma CPZ (ng/ml)</i>	<i>Platelet aggregation response (5-HT as % ADP)</i>	
		<i>Initial rate</i>	Δ OD
15	15	26.2	4.9
7	85	12.8	11.4
12	46	44.4	43.4 E
17	125	32.2	21.9
10	10	20.4	11.7
9	75	30.5	23.2
11	24	43.4	17.8
6	45	27.7	6.3
Mean	53.1	29.7	17.58
$\pm$ s.e. mean	14.0	3.78	4.39
n	8	8	8

E=enhanced 5-HT aggregation response

Data for eight out of nine patients studied in 1978 (Group 2, Table 1) in whom plasma CPZ was measured.

Aggregation responses are given as initial rate of aggregation (V_{max}) and the total change in optical density of platelet-rich plasma (Δ OD) as described by Boullin *et al.* (1975) and Orr & Boullin (1976).

that CPZ therapy affects megakaryocytosis to produce an abnormal population of platelets which show enhanced responses to 5-HT. If CPZ therapy is long-term then effects may disappear. We have evidence from animal experiments (Boullin, Bromley, Grimes & Starling, unpublished observations) and also with human platelets (Boullin *et al.*, 1975) that 5-HT enhancement is not a direct effect of CPZ or of seven of its metabolites. We can produce enhanced 5-HT aggregation in goats treated chronically with 6 mg/kg CPZ i.v., and yet demonstrate inhibition of this enhancement 0.5 h after injection when plasma CPZ is very high and at its peak value. This inhibition is a direct effect since it has been known for some years that CPZ inhibits 5-HT aggregation when added to platelet rich plasma *in vitro* (Mills & Roberts, 1967). Consequently CPZ enhancement of 5-HT-induced aggregation occurs by some indirect mechanism.

The situation at present is reminiscent of the current controversy about the role of platelet monoamine oxidase (MAO) in schizophrenia (for references see Pletscher, 1978). Also it is possible that only certain patient groups are likely to be amenable to this biochemical index of the efficacy of CPZ therapy. This appears to be the case with college students, with regard to platelet MAO activity and emotional states as determined by psychiatric counselling and suicide attempts (Buchsbaum, Coursey & Murphy, 1976).

In any event it seems likely that the solution of the problem of the mechanism of 5-HT enhancement will not be easy. We hope that other investigators will report any relevant positive or negative findings.

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Received July 10, 1978

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