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LETTER TO THE EDITOR

PARACETAMOL ELIMINATION IN PATIENTS WITH TRICUSPID REGURGITATION WITHOUT CARDIAC FAILURE

Sir,

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The congestive cardiac failure (CCF) has variable effects on drug kinetics (1). Hepatic metabolism of drugs was reported to be impaired in CCF as evidenced by decreased elimination of aminopyrine (2), theophylline (3) and antipyrine (4). However, a study with frusemide suggested unaltered metabolism of drugs in CCF (1). Recently we have reported that paracetamol elimination was impaired in patients with CCF having bilateral pedal/presacral oedema (5). It suggested that impairment of paracetamol elimination in CCF may be due to decreased hepatic microsomal enzyme activity or related to increased volume of distribution of the drug due to fluid retention. We have carried out the present study in patients with functional tricuspid regurgitation without cardiac failure, who had attained dry weight, so that the effect of the cardiac disease *per se* on paracetamol elimination could be assessed.

The study was done in six patients (4 male, 2 female) who had rheumatic heart disease and functional tricuspid regurgitation without failure and 6 male healthy volunteers. Their mean (±SEM) age was 24.6±1 2 and 30.8±2 8 yrs and their mean (±SEM) body weight was 37.6±1.9 and 58.8±2.2 kg for cardiac patients and healthy volunteers respectively. We have chosen patients who were on decongestive therapy (tablet digoxin, tablet frusemide and potassium chloride supplement) for a long period but still failed to show improvement with regard to jugular venous pressure (prominent 'v' wave) and hepatomegaly but had attained dry weight. The criteria for dry weight is for body weight to show a consistent value over 3 consecutive recordings of weekly intervals, while on decongestive therapy. All subjects were non-smokers, non-alcoholic and were not exposed to any other drugs known to alter drug metabolism. They have given informed consent and the study was approved by local Ethics Committee.

The paracetamol study was done on the second day of admission. After overnight fast 1 gm of paracetamol (2 tablets, 0.5 g each) was given orally at 06.00 hr. Food was withheld for the next 2 hr to ensure complete absorption. Samples of saliva were collected at 0,2,3,4,5 and 6 hr for the measurement of paracetamol. Nothing was given orally 30 min prior to saliva collection. The salivary paracetamol concentration was determined on the same day by a spectrophotometric method (6). The sensitivity of the method was 1 μg/ml. A standard curve prepared over the range of 2.5 to 40.0 μg/ml was used for reading the unknown concentration. The pharmacokinetic calculations were done assuming complete absorption and mono-exponential elimination of the drug as described earlier (5). The student 't' test was used for statistical analysis

In patients with tricuspid regurgitation, the salivary paracetamol half-life was significantly prolonged ($P<0.01$) when compared to healthy volunteers suggesting impairment of microsomal enzyme activity. The volume of distribution of the drug is also significantly higher ($P<0.01$) in them (Table I). This may be partly due to the underweight of the patients; since an earlier study showed that

TABLE I : Paracetamol kinetics in patients with tricuspid regurgitation.

No.	*Half-life (hr)*	*Volume of distribution (l/kg)*	*Clearance rate (ml/min/kg)*
1	3.5	1.18	3.89
2	2.6	0.94	4.16
3	2.4	1.08	5.20
4	2.6	0.99	4.40
5	2.8	1.34	5.53
6	2.5	0.70	3.23
Mean±S.E.M.	2.8** ±0.2	1.04* ±0.09	4.40 ±0.35
Healthy volunteers (n=6)	1.6	0.69	4.31
Mean±S.E.M.	±0.1	±0 05	±0.43

*P<0.01, **P<0.001 when compared with healthy volunteers

volume of distribution of phenylbutazone was increased in undernourished subjects (7). However, there was no significant change in clearance rate which could be due to increase in volume of distribution of the drug offsetting the effects of changes in paracetamol half-life. The above results are similar to our earlier observation in patients with cardiac failure having pedal oedema (5). In contrast to the patients involved in the earlier study (5), the patients of the present study did not have pedal or presacral oedema and were receiving decongestive therapy for long periods. Still, the paracetamol elimination was found to be decreased in them as evidenced by increased elimination half-life of the drug. This might be due to persistently elevated venous pressure resulting in chronic venous congestion of the liver which is known to decrease the metabolism of drug (1).

We conclude based on the results of the present study and our earlier data (5) that decreased hepatic microsomal enzyme activity may be mainly responsible for the impairment of paracetamol elimination in patients with elevated venous pressure as in chronic tricuspid regurgitation and chronic congestive cardiac failure.

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