THE ABSORPTION CHARACTERISTICS OF PARACETAMOL TABLETS IN MAN

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Paracetamol tablets from different sources showed widely differing absorption patterns in man. As judged by a blood concentration at 45 min. of less than 10 μg./ml. whole blood, low absorption was usually found in 25 per cent of subjects. This may be reduced to less than 10 per cent by a new paracetamol/sorbitol tablet. This combination produced higher average blood levels at 45 min. than crushed tablets of paracetamol. There appears to be a relation between the absorption of the drug and both age and weight; this variation can be reduced by paracetamol/sorbitol.

THE work of Lester and Greenberg (1947) and Brodie and Axelrod (1948, 1949) established that paracetamol is the metabolite of acetanilide and phenacetin which is responsible for the analgesic and antipyretic effects of these compounds. Subsequently, paracetamol was studied by Clark (1951), Batterman and Grossman (1955), Carlo, Cambosos, Feeney and Smith (1955), Cornely and Ritter (1956), Orkin, Joseph and Helrich (1957) and Weikel (1958). Its absorption characteristics in man have now been further investigated.

METHODS

Analytical Procedure

The analysis of non-conjugated paracetamol in whole blood was made using the method of Gwilt, Robertson and McChesney (1963).

Organisation of Panel

Because of the large number of venopunctures required, several panels of human volunteers were obtained from a large available population of both sexes between the ages of 20 and 50. There were 20 subjects in Panel 1, 52 in Panel 2, 144 in Panel 3 and 54 in Panel 4. A more detailed study of blood concentrations was made on Panel 4 and its composition is therefore given below.

COMPOSITION OF PANEL 4, 26 MALES, 28 FEMALES

Age

20–25 yr.	25–30 yr.	30–35 yr.	35–40 yr.	40–45 yr.	45–50 yr.
7	17	7	7	7	9

Weight

7–9 st. (44–57 kg.)	9–11 st. (57–70 kg.)	11–13 st. (70–83 kg.)	13–15 st. (83–95 kg.)
8	26	14	6

Administration of Drug

Volunteers were instructed to take no medication in the 24-hr. period before the experiment. A random sampling showed that paracetamol was absent at the beginning of the experiment. A standard product was needed as a reference and therefore the most widely prescribed preparation of paracetamol was selected (Product P). Two 0·5 g. tablets were taken whole or powdered (No. 12 mesh) with 100 ml. of water. The drug was taken either on an empty stomach or 1–2 hr. after a breakfast of cereal, toast and a beverage. In comparative studies, tablets were given on successive days at the same time after the meal. Unless otherwise specified, all experiments were made after this standard meal.

At various intervals after taking the drug, 5 ml. samples of venous blood were withdrawn from the arm and immediately transferred to an oxalated container and shaken. The analysis was then made on a 2 ml. sample as soon as possible, the remainder of the blood being kept for duplicate assay where necessary.

RESULTS

Using the 20 subjects in Panel 1, blood samples were withdrawn at 0·5, 1, 1·5 and 2·5 hr. after taking the drug. The average blood concentration at each of these times with their standard errors is shown in Fig. 1.

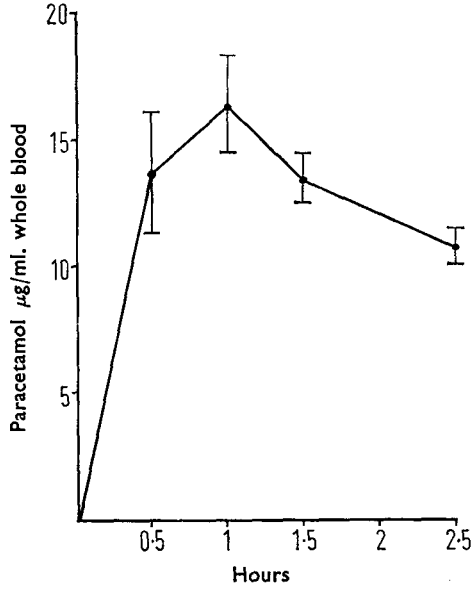

FIG 1. Average blood level (20 subjects) with ± s.e. Dosage 1000 mg. paracetamol as tablets (Product P).

The highest average concentration in the blood was reached between 30 and 90 min. As individual peak times varied, an arbitrary standard time of 45 min. was selected for future comparisons.

Absorption Distribution of Paracetamol

The standard dose of the drug (1 g.) was taken by the 144 subjects in Panel 3, blood samples being withdrawn at 45 min. after administration. The results are shown in Fig. 2 as a coarsely grouped histogram. The

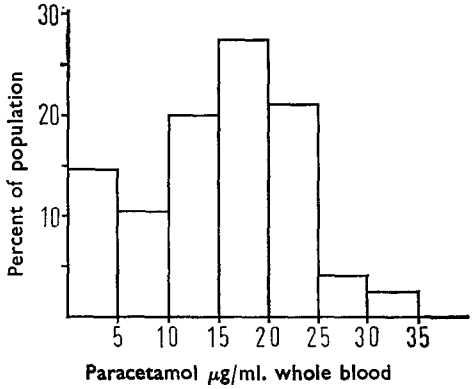

FIG. 2. Blood level distribution after administration of 1000 mg. paracetamol as Product P (144 subjects).

mean concentration was found to be 16 μg./ml. whole blood (s.e. 0·60). The results were further grouped into quartiles with approximate ranges of 0–10 μg./ml. (first quartile), 10–20 μg./ml. (second and third quartiles), over 20 μg./ml. (fourth quartile).

The second and third quartiles represent an approximate range of the mean of the whole distribution ± one standard deviation.

On this basis, it was inferred that blood concentrations below 10 μg./ml. and above 20 μg./ml. whole blood probably represented poor and high absorption respectively. The low blood levels were not due to rapid excretion of the drug (unpublished observations).

Thirty-five of the panel of 144 subjects (24 per cent) would therefore appear to be low absorbers of paracetamol.

Blood Levels After Taking Other Paracetamol Tablets

Because of the high proportion (24 per cent) of subjects with a blood concentration of less than 10 μg./ml., seven other paracetamol products were studied. Samples of these, labelled K to R, were assayed for their physical characteristics. Weight, disintegration time and content of drug were within the limits recently laid down for the official B.P. standard.

Using Panel 2, each product, equivalent to 1 g. of drug, was given to each subject at a standard time, a single blood sample being withdrawn at 45 min. The means and standard errors are shown in Table I. The results indicate that most of the paracetamol products produced a mean blood concentration at 45 min. of 15–16 μg./ml. 95 per cent confidence limits for the means of the 8 products tested are 2·02 μg./ml. and there is obviously no significant difference between the means of Products L, M,

TABLE I

MEAN BLOOD LEVELS, μG./ML. WHOLE BLOOD, 45 MIN. AFTER ADMINISTRATION OF EIGHT PARACETAMOL PREPARATIONS IN A DOSE OF 1 G. EACH RESULT IS AN AVERAGE OF 45 SUBJECTS

Product	Mean, μg./ml.	Standard error, μg./ml.
K	12·6	0·75
L	15·0	0·94
M	15·0	0·78
N	15·4	0·87
O	16·2	0·93
P*	16·0	0·60
Q	18·0	0·82
R	19·3	0·83
Grand Mean ..	15·9	0·82

* Average of 144 subjects.

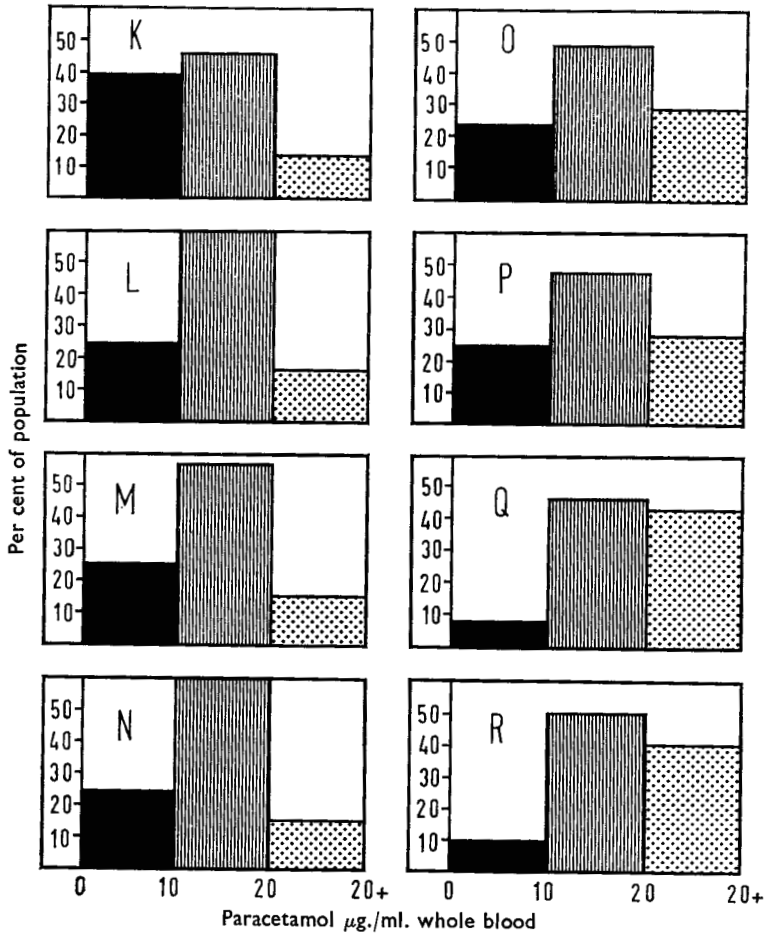

FIG. 3. Blood level distribution for eight currently available paracetamol tablets (dose 1000 mg.).

N, O and P. The mean for product K, is significantly smaller than the rest ($P<0.05$), while that for R is significantly greater than the rest ($P<0.05$); Product Q also approaches a significant difference at the 95 per cent level.

In Fig. 3, the results are shown as coarsely grouped histograms. As judged by a 45 min. blood concentration of less than 10 μg./ml. whole blood, the range of poor absorption varies from 8–39 per cent of all subjects tested. With most of the products (L, M, N, O and P), poor absorption occurs in approximately 25 per cent of subjects. Because of the marked variation in absorption of these products, a compound was sought which would reduce the percentage of poor or low absorbers.

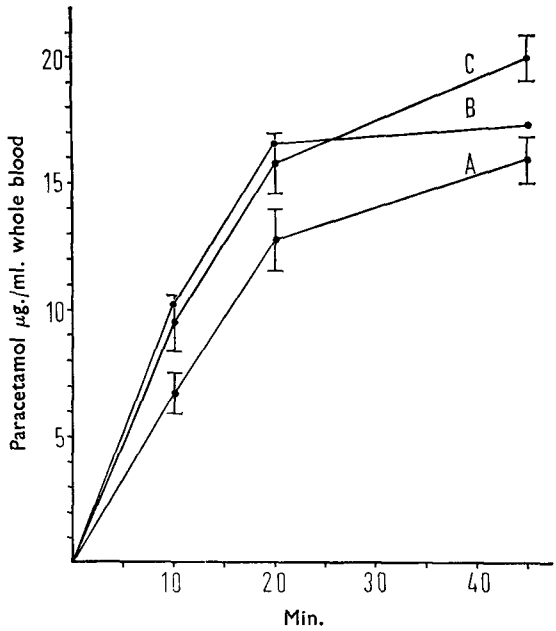

FIG. 4. Average blood levels (54 subjects) with ± s.e. for paracetamol and paracetamol/sorbitol whole tablets, 10, 20 and 45 min. after administration (dose 1000 mg.).

A, Paracetamol tablets whole.
B, Paracetamol tablets crushed.
C, Paracetamol/sorbitol tablets whole.

Studies on a New Paracetamol Tablet

It has been previously reported (Boger, Brashear and Gavin, 1959, and Herbert, Bierfass, Wasserman, Estren and Brody, 1959), that the absorption of some drugs can be increased by the hexahydric alcohol, sorbitol. Experiments were therefore made using varying amounts of sorbitol and paracetamol and, eventually, a tablet containing 500 mg. paracetamol and 100 mg. sorbitol was submitted to comparative blood studies. This new tablet had an acceptable disintegration time (B.P. method).

As variations in the results from whole tablet studies may be due purely to disintegration phenomena, a comparison of whole tablets with crushed tablets was also made. The 54 subjects in Panel 4 were used, the tablets being taken on an empty stomach. Blood samples were withdrawn at 10, 20 and 45 min. Three preparations were compared, viz., the new paracetamol/sorbitol tablet, whole, and paracetamol (Product P) whole and crushed. The order of administration of the three preparations was randomised to eliminate order effect.

The average blood concentrations for these three preparations are shown in Fig. 4, each point on the curve being an average of 54 readings, together with the standard errors for paracetamol (whole) and paracetamol/sorbitol. The results were submitted to analysis of variance to test their significance and the calculations are given in Table II. The analysis of

TABLE II

ANALYSIS OF VARIANCE BETWEEN PARACETAMOL TABLETS WHOLE, PARACETAMOL TABLETS CRUSHED AND PARACETAMOL/SORBITOL TABLETS

Source	Sum of squares	d.f.	Mean square	Variance ratio
Between subjects	11,791·94	53	(222·49)	
Between times	6,854·41	2	(3,427·20)	
Between products	1,111·85	2	(555·93)	
TxS Interaction	3,331·79	106	31·43	1·69*
TxP Interaction	291·38	4	72·85	3·91*
SxP Interaction	5,018·81	106	47·35	2·54*
TxSxP	3,949·17	212	18·63	
Total	32,349·39	485		

* Significant at $P < 0.001$.

variance of the results from 10, 20 and 45 min. samples showed that both the combination and crushed drug alone were significantly better absorbed ($P < 0.05$) than whole tablets of the drug alone at 10 and 20 min. At 45 min., however, paracetamol/sorbitol was significantly better absorbed ($P < 0.05$) than paracetamol, either crushed or whole.

As these were studies on an empty stomach, the combination was then given to the 52 subjects in Panel 2, so that a true comparison could be obtained with the results from the other products tested. Tablets were given at the same time interval after a morning meal as in other studies. The results shown in Fig. 5 in histogram form may be compared with Fig. 3.

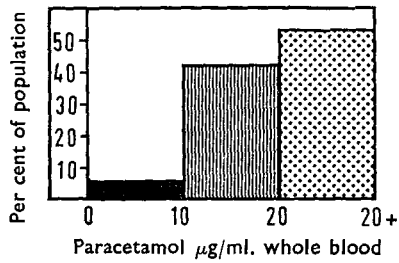

FIG. 5. Blood level distribution 45 min. after administration of paracetamol/sorbitol tablets (dose 1000 mg.). Compare Fig. 3.

With paracetamol/sorbitol the number of low or poor absorbers was reduced to 6 per cent. The average blood concentration at 45 min. was 20·8 μg./ml. whole blood (s.e. 0·84), which is significantly higher ($P < 0{\cdot}05$) than the grand mean recorded for the 8 products previously tested (Table I).

Effect of Other Variables

Weight. The results from Panel 4 (54 subjects) for the drug as whole and crushed tablets and with sorbitol as whole tablets (Fig. 4) were examined for the effect of weight. For all presentations, blood concentration was found to be lower in the six subjects weighing 83–95 kg. and higher in the eight subjects weighing 44–57 kg. The difference was further investigated by calculating regression coefficients. Each of these was found to be highly significant ($P < 0{\cdot}001$). They are expressed graphically in Fig. 6. There is obviously no difference between crushed

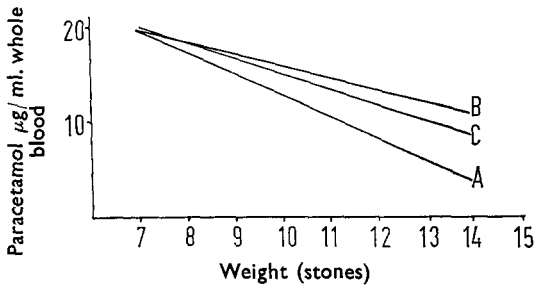

FIG. 6. Combined graph of trend lines for regression of blood level on body weight. (Dose 1000 mg.).

A, Paracetamol tablets whole.
B, Paracetamol tablets crushed.
C, Paracetamol/sorbitol tablets whole.

tablets of paracetamol and whole tablets of paracetamol/sorbitol. The difference between paracetamol whole tablets and the combination, however, approaches significance at a 95 per cent level. It may be therefore that the dependence of blood concentration on weight can be improved with crushed tablets or with the combination.

Age. Using the same data, an assessment was made of the effect of age. The results are expressed graphically in Fig. 7.

Both for whole and crushed tablets, absorption appeared poorest in the younger and older age groups and best in age groups 30–40; whereas with paracetamol/sorbitol there was an approximately linear relationship between age and blood concentration.

Dose size. To test whether a similar reduction in poor absorption could have been achieved more simply by increasing the amount of paracetamol, 1,500 mg. (as Product P) was given to 50 of the subjects in Panel 4. The tablets were taken on an empty stomach and the results compared with those previously obtained for 1,000 mg. of drug alone and with sorbitol.

As expected, increasing the dose to 1,500 mg. produced a higher average blood concentration (23·8 μg./ml. whole blood, s.e. 1·40), than either 1,000 mg. of drug or drug plus sorbitol. However, the increased dose did not reduce below 10 per cent the number of those subjects with a blood concentration of less than 10 μg./ml. whole blood.

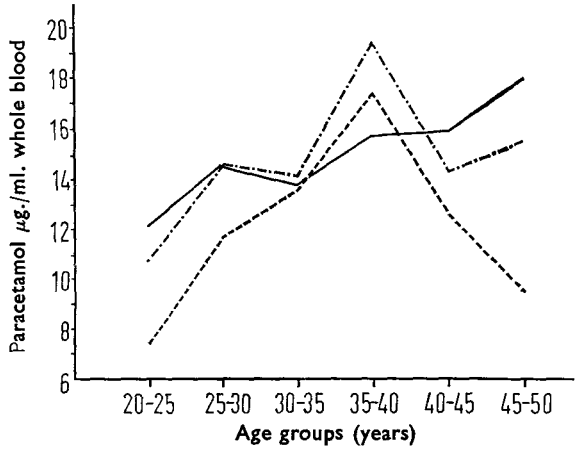

FIG. 7. Average of 10, 20 and 45 min. readings related to age groups.
———— Paracetamol/sorbitol tablets.
·—·—·—·— Paracetamol tablets crushed.
– – – – – Paracetamol tablets whole.

Stomach contents. The results on absorption from an empty stomach and after a normal meal were analysed to determine the effect of stomach contents on absorption. For whole tablets of product P the results were 15·9 and 16·0 and for the combination 20·1 and 20·8 μg./ml. respectively. There is no significant difference for paracetamol or paracetamol/sorbitol whether taken on an empty stomach or after a meal. However, the differences between drug alone and in combination under both conditions are highly significant ($P < 0.001$).

DISCUSSION

We have shown previously (Gwilt and others, 1963) that the tissue levels of paracetamol may be inferred from blood level estimations. As judged by a 45 min. blood concentration of less than 10 μg./ml., the average figure for poor absorption was about 25 per cent with various paracetamol preparations. A new paracetamol/sorbitol tablet produced higher blood concentrations than the drug alone and thus raised the blood concentrations of subjects who previously had low levels to a concentration comparable to that of subjects who absorbed the drug well. Similarly, the average blood concentration at 45 min. was found to be 20·8 μg./ml., a significantly higher level than had been obtained with ordinary tablets tested in comparable dosage.

Indeed, at 45 min., paracetamol/sorbitol was significantly better absorbed than the drug alone as crushed or whole tablets. It is interesting to speculate on these findings. If the addition of sorbitol acted merely as a dispersal agent, then the absorption patterns of the new tablet should resemble that of a crushed tablet. From our studies, it would appear that sorbitol, in addition to dispersal, acts in some way on the metabolism of the drug.

It could be maintained that the same advantage might be achieved more simply by the administration of a larger dose of paracetamol but we have shown that even in a dose of 1,500 mg., it does not reduce the percentage of low absorption more than can be achieved with the combination for a lesser dose of the drug.

Comparing the three types of medication, paracetamol whole and crushed and paracetamol/sorbitol, with respect to age and weight, there was an inversely linear effect on blood concentration with increasing weight, i.e., the heavier the subject the lower the blood concentration. Although this is what would normally be expected, this dependence could be reduced either by crushing the tablet or by using the combination. There also appeared to be a dependence on age, the best absorption with the drug alone taking place in those subjects between the ages of 30–40. With the combination, however, there was an approximately linear relation between age and blood concentration, a finding to be expected for both preparations because the metabolic rate is likely to be higher in the younger than in the older subject. There is no obvious explanation for the poor results in the younger and older subject with paracetamol.

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