Antipyrine half life and clearance in clinical practice

SIR,—The antipyrine half life has been widely used in research to assess alterations in hepatic microsomal drug oxidation. It was refreshing, therefore, to read the recent account by Dr H S Fraser and others (19 June, p 1507) of its clinical application, and we would like to record our experience of the value of this measurement in the management of two further patients. Clinical circumstances suggested that complications were arising as the direct result of enzyme induction. Measurement of the antipyrine half life and clearance confirmed this and helped to clarify the situation. After a standard oral dose (18 mg/kg) measurement of the antipyrine concentration¹ in serial mixed saliva samples was used to assess its decline during the next 24 hours.

A man of 36 with epilepsy, normally well controlled on phenobarbitone, phenytoin, and ethosuximide, developed frequent major fits within two weeks of starting rifampicin therapy for pulmonary tuberculosis. The serum steady-state phenytoin concentration measured by radioimmunoassay² was 3.6 µmol/l (0.9 µg/ml) (therapeutic range 40-80 µmol/l (10-20 µg/ml)), which suggested induction of phenytoin metabolism from the combined effects of phenobarbitone and rifampicin. Phenobarbitone is known to reduce phenytoin levels³ and rifampicin is a potent enzyme inducer.⁴ In view of the sudden deterioration in anticonvulsant control it seemed possible that rifampicin had exaggerated the phenobarbitone induction effect. Shortening of the patient's antipyrine half life to 5.17 hours compared with 12.4 ± 2.04 (SD) hours in a group of normal control subjects and a clearance rate of 86.7 ml/min (normal 40.8 ± 10.9 ml/min) provided sufficient evidence of microsomal enzyme induction. Gradual increase in the daily dose of phenytoin over a period of four weeks resulted in a therapeutically effective level of 44 µmol/l (11 µg/ml), with resolution of the fits.

A 41-year-old woman with mitral valve disease was admitted to hospital with left basal pneumonia. Nine years previously she had sustained a right hemiparesis secondary to a cerebral embolism which was also accompanied by a major epileptic fit. Phenobarbitone was started in a dose of 60 mg four times daily. In addition to the pneumonia there was clinical evidence of cardiac decompensation with an enlarged, tender liver, but there was no evidence of subacute bacterial endocarditis. Overall improvement resulted from antibiotic therapy, with resolution of the pneumonia and gradual regression of the hepatomegaly.

Biochemical investigation revealed consistently low serum calcium (1.85 mmol/l (7.4 mg/100 ml), normal 2.22-2.72 mmol/l (8.9-10.9 mg/100 ml)) and serum phosphate (0.55 mmol/l (1.7 mg/100 ml), normal 0.8-1.4 mmol/l (2.5-4.3 mg/100 ml)) levels and consistently raised alkaline phosphatase levels (280 IU/l, normal 40-115). These results, together with a low serum 25-OH-cholecalciferol level of 2.1 µg/l (normal average 12.5 µg/l) were consistent with "florid" osteomalacia, but no radiological evidence could be detected. Moderately raised aspartate transaminase and lactic dehydrogenase levels and prolonged prothrombin and partial thromboplastin times indicated mild disturbance of liver function which probably reflected hepatic congestion. The serum γ-glutamyl transpeptidase level was 94 IU/l (normal 5-25). The antipyrine half life was 8.1 ± 0.6 hours (normal 12.4 ± 2.04), with a clearance of 66 ml/min (normal 40.8 ± 10.9). Plasma steady-state phenobarbitone levels averaged 150 µmol/l (3.5 mg/100 ml), consistent with adequate anticonvulsant activity. With no history to suggest a recurrence of fits since the initial presentation phenobarbitone was withdrawn slowly and treatment with calcium and vitamin D tablets BPC instituted.

Antipyrine half-life values in these patients were consistent with induction by drugs such

as rifampicin and phenobarbitone. Confirmation of this was important as it had a direct bearing on subsequent management. In the first case adjustment of phenytoin dosage to attain therapeutically effective plasma levels had to be seen in the light of induced phenytoin metabolism which would alter the normal relationship between dose and plasma level. This was obvious when adjustment of the dose according to a published phenytoin nomogram⁵ failed to raise plasma concentrations adequately and a dose in excess of that recommended had to be employed. Proof of induction was also important as this would emphasise the need for careful reduction in phenytoin dosage on withdrawal of rifampicin therapy. Failure to recognise this would undoubtedly lead to serious phenytoin toxicity if the dose was not adjusted to suit the return to a relatively normal rate of drug oxidation.

Osteomalacia secondary to anticonvulsant therapy is well recognised⁶ and in the second case a shortened antipyrine half life served to highlight the underlying mechanism of induced vitamin D metabolism. It is interesting to note, however, that despite prolonged exposure to a daily dose of 240 mg phenobarbitone the diagnosis of osteomalacia was based solely on biochemical evidence, and the margin between the patient's antipyrine half life and that of the control group was relatively narrow. This may have been a reflection of genetically determined individual variability in the response to inducing agents.⁷ On the other hand hepatic dysfunction, due in part to cardiac failure, may have modified the liver's capacity to eliminate antipyrine.

Measurement of the antipyrine half life in individual patients by the relatively simple non-invasive technique of serial saliva collections can yield useful information on the activity of hepatic microsomal enzymes which can be utilised subsequently in both short- and long-term management.

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¹ Brodie, B. B., et al, *Journal of Biological Chemistry*, 1949, **179**, 25.

² Paxton, J. W., et al, *Journal of Immunological Methods*, 1976, **10**, 317.

³ Morselli, P. L., et al, *Annals of the New York Academy of Sciences*, 1971, **179**, 88.

⁴ Remmer, H., et al, *Drug Metabolism and Disposition*, 1973, **1**, 224.

⁵ Richens, A., and Dunlop, A., *Lancet*, 1975, **2**, 247.

⁶ Dent, D. E., et al, *British Medical Journal*, 1970, **4**, 69.

⁷ Vessell, E. S., and Page, J. G., *Journal of Clinical Investigation*, 1969, **48**, 2202.

Sociological factors and female Olympic potential

SIR,—A total of 197 separate events were contested at the Olympic Games in Montreal, yielding 609 medals. The USSR has repeated her previous performance in Munich by topping the list of leading nations with 125 of the 609 medals (table I). More than 50% of the total medals were won by the three leading nations, the USSR, the USA, and East Germany, and the reasons for the USA's failure to regain her lead were anticipated in an earlier communication (3 July, p 40).

Table I reveals interesting sex differences in the distribution of medals won by the leading nations. About a quarter of all medals

relate to women's athletic and sporting contests. The contribution of women in East Germany's pool of medals is strikingly different from those of the USSR and the USA. Of the 88 medals won by East Germany, 49 (55.7%) were won by women, and in contrast the percentages of female medallists from the USSR and the USA were 28.8 and 18.1 respectively.

TABLE I—Distribution of men's and women's medals, Montreal, 1976

	USSR	USA	E Germany	Other nations	All nations
Men	89	77	39	257	462
Women	36	17	49	45	147
Total	125	94	88	302	609
Women %	28.8	18.1	55.7	14.9	24.1

Results in tables I and II are derived from data published in *The Times*, 2 August 1976.

TABLE II—Distribution of medals in women's sporting events, Montreal, 1976

Events (Nos in parentheses)	USSR	USA	E Germany	Other nations	Total
Archery (1)*	2	1	0	0	3
Athletics (14)	8	3	19	12	42
Canoeing (2)	2	0	2	2	6
Fencing (2)	2	0	0	4	6
Gymnastics (6)	8	0	2	8	18
Rowing (6)	5	2	6	5	18
Swimming (15)	6	10	19	10	45
Team events (3*)	3	1	1	4	9
Total (49)	36	17	49	45	147

*Volleyball, handball, basketball.

It is of further interest to note that East Germany topped the list of the leading nations in women's contests. Table II shows the virtual domination of East German girls in athletics, rowing, and swimming events. Besides Kornelia Ender, who won three gold medals in the individual swimming events, there were five other girls who won two medals each. In the women's pentathlon all the three medallists were from East Germany. In the six rowing events East Germany won four gold and two silver medals. These results show that East Germany's achievements in the pool of women's medals were not entirely attributable to the chance discovery of one or two "wonder" girls in their team.

Many questions remain unanswered at this stage. How is it that East Germany, with less than a tenth of the population of the USSR or the USA, could win so many gold medals (USSR 47, E Germany 40, USA 34)? In the men's swimming events East Germany won only a single medal compared with USA's 29 and USSR's six. In the women's swimming events, however, East Germany dominated by winning 19 medals to the USA's 10 and the USSR's six. Similarly, in the men's athletic and field events East Germany won eight medals compared with the USA's 19 and the USSR's 10. But East Germany's female athletic team won 19 medals compared with the USA's three and the USSR's eight. Acceptance of the argument that selection and training methods in East Germany are very rigorous ("factory-produced" athletes) does not explain the large disproportionate contribution of their women in winning 55.7% of their 88 medals. "Factory production" methods are unlikely to be selectively biased in favour of women.

The observed sex difference suggests the importance of a complex sociocultural variable in the optimum selection of female athletic and sporting talent. It appears that other countries are failing to exploit the sporting potentialities of their women in the way that East Germany has done.

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Anti-inflammatory drugs for rheumatoid arthritis

SIR,—Clinical judgment should be based on fact rather than fantasy. This thought is provoked by the paper by Dr E C Huskisson and others (1 May, p 1048) but more particularly by the recent advert for Naprosyn which appeared as a pull-out supplement in your Journal (3 July). We would dispute the opening premise of this article, namely, that aspirin is no longer treatment of choice in rheumatoid arthritis. Out of the three references for this statement two were by Huskisson himself.

However, our major objections to this paper are not based on a matter of opinion but the following facts: (1) The tablets used were not matched, naproxen being different from the other three. (2) There are no baseline data and, moreover, no placebo group, which is so important in a short-term study. (3) There is the introduction of a new toxicity index which is neither defined nor evaluated. (4) The conclusions drawn do not appear to be justified from the data presented—namely, fenpropfen reduced morning stiffness and joint size better than the other agents, suggesting that fenpropfen was more anti-inflammatory in this study.

We believe that in this paper there are too few facts for too many conclusions and that great care should be taken in its interpretation.

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* * * We sent a copy of the above letter to Dr Huskisson and his colleagues, whose reply is printed below.—ED, *BMJ*.

SIR,—It was not our intention to present evidence that aspirin is no longer the first line of treatment for rheumatoid arthritis. Our introduction merely intended to say that if this were true it would be nice to know which of the propionic acid derivatives might have taken its place. We support the desire for fact in preference to fantasy. The facts put forward in our paper were that two of the drugs tested were more effective than the other two and that two more produced side effects. These facts were supported by statistical significance levels which are unusually high because of the large number of patients treated.

We are not impressed by the specific objections: (1) None of the tablets were matched but all were unrecognisable. We know of no evidence that colour affects the performance

of active analgesics, and for placebo, yellow is the worst colour.¹ Problems of bioavailability prevented us from using identical formulation. (2) Baseline data were collected and are available. However, the principle of a crossover trial is that a patient's state at the end of one treatment period is compared with his state at the end of another, and we cannot see the value of baseline data. Patients in trials always improve, and one could not use this improvement as evidence that the new treatment was better than the old. We did not set out to show that propionic acid derivatives were effective, which has been done, and didn't therefore need placebo. We set out only to compare the drugs. (3) Dr H Berry may remember the study of which he was a co-author,² in which side-effect scores were first used as a measure of toxicity. (4) The differences between fenpropfen and naproxen in morning stiffness and joint size were not statistically significant and there was no justification for the claim that its anti-inflammatory potency was greater.

We have examined the advertisement for Naprosyn and find the facts in it to be accurate. We regret only the omission of what for us was the most important conclusion of the study. Our trial showed for the first time that there is one particular drug which is right for one particular patient, and Dr Clarke and his colleagues may be interested to hear that for this reason some of our patients still take . . . aspirin.

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¹ Huskisson, E C, *British Medical Journal*, 1974, 4, 196.
² Huskisson, E C, et al, *British Medical Journal*, 1974, 1, 176.

Confidence limits

SIR,—In his article "Statistics at Square One, XI—The *t* tests" Dr T D V Swinscow (31 July, p 291) falls into a trap which many of us are at pains to warn our students about. After finding the 95% confidence limits for a population mean to be 120.97 and 109.03 he writes, "We therefore conclude that the chance of the population mean lying below 109.03 or above 120.97 is only 5% or less." The "or less" is, on any interpretation, redundant and misleading, but the major point is that the standard theory of confidence limits does not allow this conclusion. The correct interpretation is that if the unknown population mean were to lie below 109.03 or above 120.97 then, on his data, an event with a chance of only 5% must have happened: either the mean lies between those limits, or something rather improbable has happened, and we usually prefer to assume the former.

In fact there is a very ingenious argument, known as the fiducial argument, advanced by Sir Ronald Fisher from 1930 onwards, which purports to justify statements of the kind made by Dr Swinscow. But it is not generally accepted by statisticians, least of all those who advocate confidence limits. Oddly enough its origins can be traced back to the very paper by "Student" that Dr Swinscow quotes, but

in general it is prudent to avoid making any statement about the probability of the population mean lying in an interval and to warn students away from it. There is deep water all round.

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* * * Dr Swinscow writes: "Dr Edwards is correct in his interpretation. The lapse is theoretical rather than practical in its implications but will be repaired when the article is revised for publication in book form later this year. I am grateful for the correction—italics and all."—ED, *BMJ*.

Accidental injection of Immobilon

SIR,—A few weeks ago the product licence for Immobilon—a potent veterinary neuroleptanalgesic combination of the opiate etorphine hydrochloride and a phenothiazine, acepromazine or methotrimeprazine—was suspended on the advice of the Veterinary Products Committee following the death, due to accidental self-injection of Immobilon, of a member of the veterinary profession.¹ In this case the recommended accident procedure, which involves the injection of a narcotic antagonist, was not followed. In other cases when accidental injection has been promptly treated by injection of a suitable antagonist recovery has been uneventful.²⁻⁵

After consideration of the circumstances of this accident and the evidence on the use of Immobilon during the past six years the Veterinary Products Committee has now recommended the reinstatement of the product licence and the recommendations for the treatment of accidental injection have been revised. The product is now again available.

It is possible that doctors may be called to treat cases of accidental administration of Immobilon and it is therefore essential that all doctors are aware of the correct treatment and have the appropriate antagonist to hand. The revised procedure recommends the use of naloxone but allows for the emergency use of nalorphine and Revivon (diprenorphine hydrochloride), the veterinary antagonist which always accompanies Immobilon. The following accident procedure appears on the reverse of the pack and also in the product literature.

ACCIDENT PROCEDURE—IMMOBILON

Immobilon is a very potent neuroleptanalgesic with a high toxicity in man. In the event of accidental administration to man, or if there is a possibility that absorption may have occurred, the procedure given below should be adopted. Symptoms caused by Immobilon are dizziness, nausea, and pin-point pupils, followed by respiratory depression, fall in blood pressure, and cyanosis. In extreme cases loss of consciousness and cardiac arrest occur.

SUMMON MEDICAL HELP IMMEDIATELY

If there is any danger that absorption of Immobilon may have occurred INJECT A REVERSING AGENT IMMEDIATELY.

(1) *Spillage on skin or splashing of eyes.* Wash immediately with copious quantities of water.

(2) *Accidental injection.* Inject one of the following reversing agents: (i) 1 ml Narcan (0.4 mg naloxone) intravenously or intramuscularly. Repeat at 2–3-min intervals if symptoms are not reversed. (ii) If Narcan is not available inject 1 ml Lethidrone (10 mg nalorphine) intravenously or intramuscularly. Repeat at 5-min intervals if necessary up to a total of 4 ml. There are Lethidrone formulations