PAPERS AND ORIGINALS

Gastric Bleeding and Benorylate, a New Aspirin

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Summary

Benorylate (4-acetamidophenyl 2-acetoxybenzoate) is a new esterified aspirin preparation whose antirheumatic properties are reported to be as good as those of aspirin. Gastrointestinal blood loss, measured with ^{51}Cr-labelled red cells, during benorylate therapy was compared with that during therapy with soluble aspirin in 15 subjects, a simplified crossover procedure being used. Mean blood loss during benorylate therapy was 1·7 ml/day which was significantly less than that during therapy with soluble aspirin (5·1 ml/day; P <0·001). In 12 of the 15 patients blood loss with benorylate was less than 2·5 ml/day. Benorylate appears to be a definite improvement on current formulations of aspirin and should be a useful drug for the treatment of patients with chronic rheumatic disorders.

Introduction

Aspirin is one of the safest and most useful of drugs. Its gastric effects are a problem in Great Britain, however, because of the large quantity of this drug that is consumed. A recent survey indicated that four and a half million people took aspirin at least once a week and that half a million took more than five aspirin tablets a day. The risk to an individual of a serious aspirin-induced gastric haemorrhage is very small, but when consumption of the drug by the community is so vast even a small risk becomes an important problem. In recognition of this the Committee on Safety of Drugs (1971) recently stressed that in its view preparations containing aspirin should not be recommended for the relief of stomach disorders, including gastric upsets and heartburn.

Probably one-quarter of all cases of haematemesis and melaena in Great Britain are precipitated by aspirin (Parry and Wood, 1967; Valman *et al.*, 1968; Croft, 1970). This represents about 7,000 admissions to hospital a year (Schiller *et al.*, 1970). From other data it can be calculated that with continuous ingestion 1 g of aspirin a day causes about 1 ml of blood loss (Wood *et al.*, 1962; Croft and Wood, 1967). If this figure is applied to the whole community aspirin consumption can be said to be responsible for the gastrointestinal loss of more than 20,000 gallons (90,000 l.) of blood a year—enough blood to fill a domestic swimming pool. This chronic blood loss can cause iron-deficiency anaemia, although the extent to which this is a community problem has not been defined.

It is important, therefore, to produce and study formulations of aspirin that may be less harmful to the stomach. The ^{51}Cr-labelled red cell technique is the most accurate means of studying the gastric effect of aspirin, as it is possible by its use to measure blood losses as small as 1·0-2·0 ml/day. It has been shown with this technique that between 70 and 90% of patients taking aspirin continuously lose more than 2 ml/day (Scott *et al.*, 1961; Wood *et al.*, 1962; Croft and Wood, 1967). Soluble aspirin causes as much bleeding as plain aspirin, and other preparations, such as choline salicylate (Cuddigan *et al.*, 1971), are no better. The simultaneous administration of a large quantity of alkali is associated with less bleeding, as is the use of enteric-coated and delayed-release preparations.

Benorylate, 4-acetamidophenyl 2-acetoxybenzoate, is a new lipid-soluble ester of acetylsalicylic acid and *N*-acetyl *p*-aminophenol. It is an odourless, tasteless compound which is well absorbed from the gastrointestinal tract. Animal studies have shown that it has anti-inflammatory, analgesic, and antipyretic properties comparable with those of aspirin and that its activity is more prolonged (Rosner *et al.*, 1971). In addition, excellent gastrointestinal tolerance in both rats and dogs was noted. With the approval of the Dunlop Committee preliminary trials have been undertaken with benorylate in the treatment of rheumatoid arthritis. Clinically the drug is reported to be as effective as aspirin as an antirheumatic drug (Sperryn *et al.*, 1971; Beales *et al.*, 1972).

The present study was undertaken to compare occult gastrointestinal bleeding in patients taking benorylate with that in the same patients while taking soluble aspirin by a new and simplified clinical procedure that we have developed (Cuddigan *et al.*, 1971).

Patients and Methods

Seven men and 13 women attending an outpatient clinic for rheumatic complaints agreed to co-operate, the nature of the

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study having been explained to them. Their ages ranged from 21 to 73 (mean 52) years. Patients with a history of aspirin intolerance, peptic ulceration, or haemorrhoids detectable by rectal examination were excluded. According to a random code which was unknown to the physician and the physicist each patient was asked to take either 10 ml of a 40% suspension of benorylate twice daily or 4 tablets (1·2 g) of soluble aspirin dissolved in water four times daily for one week. The alternative drug was then substituted and was taken for a further week. Blood samples were taken at the end of each treatment week and assayed for benorylate and aspirin to confirm that the relevant preparation had been taken.

At their first attendance samples of the patients' red blood cells were labelled with ^{51}Cr and reinjected, further samples being taken for radioactivity counting at 15 minutes and one and two weeks. Stools were collected on each of the last four days of each week of treatment, the radioactivity was measured with a modified plastic scintillation whole-stool counter (Clapham and Hayter, 1962), and the volume of blood in each stool was calculated. The details and validity of the technique have been published elsewhere (Cuddigan *et al.*, 1971).

Results

Five patients were excluded from the analysis because of incomplete stool collections, intercurrent illness, or failure to take the drugs. From the remaining 15 patients 121 stools were received. Previous work suggests that a mean daily blood loss of more than 2 ml/day should be regarded as clinically significant for this method (Croft and Wood, 1967; Cuddigan *et al.*, 1971). The mean daily blood loss with aspirin was 5·1 ml (S.D. 4·3) and with benorylate 1·7 ml (S.D. 1·6) (see Table). The difference

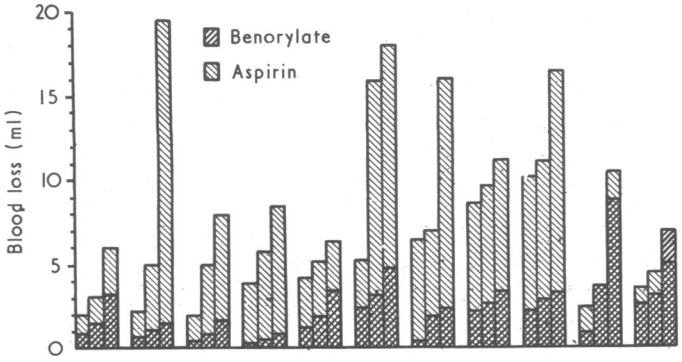
Blood Loss (ml/day) in 15 Patients During Treatment with Soluble Aspirin and Benorylate in Alternate Weeks

Treatment	Week 1	Week 2	Total
Soluble aspirin ..	4·4	5·7	5·1* (S.D. 4·3)
Benorylate	1·8	1·7	1·7* (S.D. 1·6)

*P <0·001.

was statistically significant (P <0·001). Of these 15 patients, four showed no significant bleeding with either preparation. If these patients are excluded the mean daily blood loss with benorylate was 2·1 ml (S.D. 1·71), which was still significantly less than that with soluble aspirin (6·8 ml, S.D. 4·6; P <0·001).

In the 11 patients who bled, the amounts lost during aspirin and benorylate treatment are represented in the Chart. In nine of the 11 patients bleeding was more heavy and more frequent with aspirin. No patient bled more frequently or more heavily



Stool blood loss in ml/day in 11 patients given aspirin for one week followed by benorylate for one week or vice versa. The three highest values of blood loss for each patient when taking aspirin are superimposed on the three highest values for the same patient when taking benorylate. Thus each group of three histograms represents one patient.

with benorylate. Two patients' blood loss was almost equal with the two drugs. They were recalled and a further stool collection was made after all therapy had been withdrawn, no bleeding was detectable in either patient. We conclude therefore that in these two patients bleeding was caused by both aspirin and benorylate.

Discussion

The ^{51}Cr-labelled red cell method is the most accurate way of measuring drug-induced gastric bleeding. We have simplified the procedure used by Scott *et al.* (1961) to produce a convenient outpatient procedure (Cuddigan *et al.*, 1971). As only eight stool specimens are collected and the patient has to attend hospital on only three occasions, rheumatological outpatients, who are at greater risk from salicylate therapy, can be readily studied. With the crossover procedure each patient acts as his own control and it is possible to compare the effects of a new drug with that of soluble aspirin. Any trial in which such a comparison is not made may give misleading results, since not all subjects are susceptible to aspirin-induced bleeding. We have found the method described above to be reliable.

The results of this study indicate that occult bleeding is an infrequent complication of benorylate therapy. The drug compares well in this respect with all salicylate preparations previously examined, and the mean blood loss of the 15 patients during benorylate therapy was within the normal range at 1·7 ml/day. Two patients did, however, show a definite increase in their blood loss during benorylate therapy. In the 11 patients who bled there was no correlation between the amounts of bleeding on aspirin and on benorylate (r = 0·50).

This study lends further support to the view that with regard to occult drug-induced gastric bleeding three groups of subjects can be distinguished (Croft and Wood, 1967). Firstly, those who do not bleed and who make up some 10% of the population. Secondly, the majority (80%), who are sensitive to aspirin and lose 2-10 ml of blood/day. It is this group who do not bleed with benorylate, as is shown in the study. Finally there is a group (10%) who are particularly susceptible to gastric irritants and lose more than 10 ml/day when taking aspirin. One would expect that these subjects might also be susceptible to less irritant drugs such as benorylate. Thompson and Anderson (1970), when studying Ibuprofen, which is generally believed to have little gastric effect, found some evidence of blood loss during treatment. At least two of their patients lost more than 2 ml daily, and in one the loss reached 6 ml; this was a patient who was also sensitive to aspirin. Thus even if a drug is shown to be substantially better than soluble aspirin in regard to bleeding, there will be some individuals who are susceptible to it.

One cannot draw direct conclusions about acute gastric haemorrhage from results obtained by measuring occult bleeding. However, it seems reasonable to believe that a drug that causes less occult bleeding than aspirin is also less likely to precipitate acute haemorrhage. Clearly other factors affect the susceptibility of the gastric mucosa to insults (*British Medical Journal*, 1970) and need to be elucidated by further research.

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Continuous Intragastric Milk Feeds in Infants of Low Birth Weight

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Summary

In a feeding trial 66 infants of low birth weight received continuous intragastric milk feeds from the fourth hour of life, starting with 60 ml/kg/24 hr and reaching a maximum of 300 ml/kg/24 hr on the ninth day. Each infant received only full-strength milk, which was either expressed human breast milk or SMA-S26 (a proprietary low-protein adapted cows' milk) or half-cream Regal milk (partly-skimmed evaporated cows' milk). For various reasons 10 babies had to be withdrawn, and the final assessment was made on the 56 who completed the trial successfully.

Persistent vomiting was a problem in only four infants. In two of them the trial was continued after gastric lavage and in the other two vomiting stopped when the volume was reduced. Despite a careful search no evidence was found of aspiration of feeds in any infant. Continuous intragastric milk infusion was shown to be a safe method of feeding infants of low birth weight and SMA-S26 was almost as well tolerated as human milk. Because of the high-protein content of half-cream cows' milk preparations and the resultant high plasma amino-acid levels when they are given in these large volumes they should be avoided for this type of feeding although they produce better weight gains in the first week of life.

Introduction

The most important controllable factors determining the survival and normal development of the newborn infant weighing 2,500 g or less are adequate food (Drillien, 1964; Davies and Russell, 1968) and warmth (Buetow and Klein, 1964; Day *et al.*, 1964; Daily *et al.*, 1969). The optimum environmental temperatures for various birth weights have been carefully assessed (Scopes and Ahmed, 1966; Hey and Katz, 1970) but the best method of feeding such small infants is still the subject of controversy.

Tube feeding is necessary for the very small infant because of the danger of aspiration consequent on the absence of normal sucking, swallowing, and cough reflexes. Movement of the diaphragm is easily impeded by gastric distension, so that intermittent tube feeds need to be of small volume and given at frequent intervals, and this is extravagant of nurses' time. It has been stated that a generous protein and energy intake is necessary to obtain optimal growth in infants of low birth weight (Gordon *et al.*, 1947; Young *et al.*, 1950; Davidson *et al.*, 1967). One cannot say with certainty what is the optimal weight gain for these infants, but it should enable babies whose weight is "appropriate for dates" to return to their initial centiles within a few weeks and most babies "light for dates" to cross the lowest centile lines. This is not achieved by the energy intakes recommended by Gordon *et al.* (1947), (Babson, 1970), but the provision of an adequate energy intake with milk alone entails the administration of such large volumes that it has become popular to use concentrated feeds (Combes and Pratt, 1961). However, water balance is a primary consideration in infant feeding when the diet gives a high renal solute load, and concentrated feeds can be dangerous (Ziegler and Fomon, 1971).

Human milk is such a safe and well-tolerated feed that many paediatricians would prefer it for feeding small babies if there was an acceptable method of administering large volumes safely. The use of continuous intragastric drip feeding with expressed breast milk was suggested by D. Hilson (personal communication) in 1960 and was given a trial in the premature baby unit of this district hospital. The results were so satisfactory that it came to be used as a routine in the unit. Before advocating the widespread use of this type of feeding we thought it desirable to carry out a critical assessment of its safety. At the same time we decided to determine whether two other liquid milks, a proprietary low-protein adapted cows' milk (SMA-S26) and a partly-skimmed evaporated cows' milk preparation (half-cream Regal),* would prove satisfactory substitutes when human milk was in short supply.

Patients and Methods

Infants weighing between 1,000 and 2,100 g at birth entered the trial at the age of 4 hours. At first infants who developed signs of severe respiratory distress syndrome before 4 hours were given 10% dextrose with sodium bicarbonate by continuous intragastric drip and were therefore excluded from the trial. Later such infants were included in the trial but the sodium bicarbonate was added to the milk.

Most of the babies were divided by random selection, using sealed envelopes, into three groups, receiving respectively: (1) expressed breast milk, (2) SMA-S26, and (3) half-cream Regal milk. Being anxious not to discourage breast-feeding, however, we advised mothers who wished to breast-feed to express their milk, and their babies were included in group 1. As a result group 1 was larger than the other two. Fifty-six

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* No longer available.