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GASTRO-INTESTINAL BLOOD LOSS IN ASPIRIN THERAPY

It is now well known that the taking of aspirin often leads to the presence of occult blood in the faeces. Recent investigations have shown that it occurs in 60 or 70% of patients undergoing aspirin therapy.[1,2] The amount of blood lost varies widely. In 38 patients given 3 G. of aspirin a day for 3 - 6 days the occult loss was less than 2 ml. a day in 15, between 2 and 5 ml. in 16, and more than 5 ml. in 7.[3] In one case recorded by Stubbé[2] it amounted to 82 ml. a day. When aspirin is taken regularly in large doses, for rheumatic complaints for instance, the occult blood loss sometimes results in serious iron-deficiency anaemia. The occult loss is to be distinguished from the haemorrhage that aspirin sometimes induces with peptic ulcer or gastritis. There appears to be no association between dyspepsia and the occult bleeding induced by aspirin. Some patients who experience severe dyspepsia after aspirin have no occult bleeding and others with considerable occult bleeding develop no gastro-intestinal symptoms.[1]

Several workers have searched for a preparation with the analgesic and anti-inflammatory properties of aspirin, but free from the tendency to cause occult bleeding. Investigations on these lines are reported in the *British Medical Journal* of 10 March 1962; these investigations have been carried out in the rheumatology departments of the Postgraduate Medical School, London (by Wood, Harvey-Smith and Dixon[1]) and of the University Hospital, Leyden, The Netherlands (by Stubbé, Pietersen and v. Heulen[2]). Stubbé *et al.* used the benzidine reaction for the demonstration of occult blood in the faeces. Wood *et al.* measured the quantity of blood by estimating the radioactivity of the faeces of patients in whom the erythrocytes were labelled with radioactive chromium (^{51}Cr) — apparently a more sensitive technique.

Wood *et al.* compared the blood loss when the preparation under test was administered with the loss in the same patient when ordinary aspirin tablets were given. Ordinarily 15 gr. (972 mg.) of aspirin, or its equivalent in the preparation under test, 4 times a day after food, was given for 5 days. Lower dosage was occasionally necessary because of salicylism, but all comparisons were made with equivalent doses. The method of administration followed the manufacturers' instructions; ordinary aspirin was given as whole tablets. It was concluded that whether the administration of the aspirin preceded that of the preparation under test, or *vice versa,* did not affect the results.

In Stubbé's experiments the patients' diet was kept free of meat and green vegetables, preparations containing iron were forbidden, and the patients were not allowed to brush their teeth. Except for coated tablets, the tablets under trial were always given with water or milk after meals. The quantity of aspirin given was 1,500 or 3,000 mg. a day. Plain aspirin was first administered, and, when the benzidine reaction was distinctly positive in 3 successive lots of faeces, the aspirin was replaced by the preparation under test in the same dosage. If and when the benzidine reaction then became negative 3 times in succession (5 times when coated aspirin tablets were being tested), it was assumed that the preparation did not cause occult bleeding. Should it not immediately become negative, however, the patient was given neither aspirin nor the preparation under test, and then unless the reaction became negative 3 times running the case was not included in the test group (this was in order to exclude other causes of occult blood loss). In these tests a reaction that was alternately negative and 'trace positive' or 'slightly positive' was counted as doubtful.

Wood *et al.* found no significant differences between the degrees of bleeding observed after aspirin B.P. and other formularies of acetylsalicylic acid studied ('aspro', 'anadin', Beecham's powders, APC, and codeine compounds — including 'codis' and 'veganin'). With soluble aspirin (calcium aspirin, disprin), freshly dissolved in water, in 31 patients they found no significant difference in the amount of blood loss, as compared with ordinary aspirin. This was in accordance with the findings of earlier workers; and in the present research Stubbé *et al.* found that the benzidine reaction became negative in only 5 out of 14 patients who were given soluble aspirin.

Wood *et al.* also found no significant difference from aspirin BP with calcium aspirin urea (dissolved in water — 15 patients), aspirin glycine (whole tablets — 15 patients), or aspirin anhydride (whole tablets — 22 patients). Stubbé's preliminary tests with these quickly disintegrating tablets were also unfavourable, for, of the small number of patients tested with each of these, in some the benzidine reaction did not become negative.

Both Wood *et al.* and Stubbé *et al.* obtained favourable results with effervescent aspirin ('alka-seltzer'). These aspirin tablets contain citric acid with a large excess of sodium bicarbonate. Wood *et al.* found that, given in water to 15 patients, they resulted in a mean blood loss of 2·5 ml. per day of treatment, as compared with 5·5 ml. when plain aspirin was given. This is a significant difference ($P < 0{\cdot}02$), and the result is confirmed by Stubbé *et al.*, who found that, of 32 patients tested with this preparation, the benzidine reaction disappeared in 31, and in the remaining one it was much weaker than during the use of ordinary aspirin. These patients of Stubbé's received 10 alka-seltzer tablets a day, equivalent to 3 G. of aspirin and 20 G. of sodium bicarbonate.

Wood *et al.* obtained favourable results with a new preparation, aloxiprin (polyoxo-aluminium-aspirin, 'pal-

aprin') — an insoluble neutral compound of aluminium aspirin in polymeric form. Given as whole tablets, it was tested in 2 series of cases. In the 1st series, of 22 patients, it resulted in a mean blood loss of 4·0 ml. per day of treatment, as compared with 7·3 with ordinary aspirin ($P < 0.01$). In the 2nd series, of 21 patients, the mean daily loss was 3·2 ml., as compared with 6·7 with aspirin ($P < 0.001$). Aloxiprin was as satisfactory as aspirin in the control of rheumatoid arthritis. No tests of aloxiprin are recorded in Stubbé's paper.

Stubbé *et al.* experimented with coated aspirin tablets. The results achieved with commercially produced tablets coated with gluten 'gave little hope',[2] but favourable results were obtained with aspirin tablets which had been coated with cellulose acetate-phthalate (CAP) at the University Hospital, Leyden. Of 30 patients treated with 250 mg. aspirin tablets coated with about 40 mg. of CAP, in 26 the benzidine reaction disappeared, in 1 it became alternately negative and trace positive (having been strongly positive with non-coated aspirin tablets), and in 3 it remained slightly positive (though much less so than with the non-coated tablets). Urine examination of all the test patients showed that the CAP coated tablets were absorbed. The effect of the coating is attributed to its remaining intact in the acid gastric juice and disintegrating when it reaches the bowel. Experiments with 4 volunteers showed the same level of free salicylate in the blood plasma as with plain aspirin. Owing to slow absorption the analgesic effect of the CAP tablets is delayed. No tests of coated tablets are recorded by Wood *et al.*[1]

As regards freedom from occult bleeding, Stubbé *et al.* got good results with salicylic preparations containing no acetylsalicylic acid ('antidol' tablets and sodium salicylate tablets); the benzidine reaction disappeared in all the patients treated. The analgesic effect, however, according to the patients, was less than that of aspirin tablets.

It is noteworthy that in these two researches[1,2] the occurrence of occult bleeding appeared to be independent of whether the acetylsalicylic acid was swallowed as such in solid form or as acetylsalicylate in solution.

In summary, the three preparations that were found to give the most promising results from the point of view of freedom from occult haemorrhage were CAP coated aspirin tablets, aloxiprin tablets, and effervescent aspirin tablets.

1. Wood, P. H. N., Harvey-Smith, E. A. and Dixon, A. St. J. (1962): Brit. Med. J., 1, 669.
2. Stubbé, L. Th. F. L., Pietersen, J. H. and v. Heulen, C. (1962): *Ibid.*, 1, 675.
3. Matsumoto, K. K. and Grossman, M. I. (1959): *Op. cit.*[1]

VERDERE ASPEKTE VAN PADONGELUKKE

Ons het by 'n vorige geleentheid die implikasies van die gebruik van sekere terapeutiese middels van verskillende aard bespreek ten opsigte van die moontlike verband tussen die gebruik van dié middels en 'n verlaging van die ‚veiligheidsdrempel' by motorbestuurders. Ons het toe aangetoon hoedat daardie aspek van die probleem van padongelukke in werklikheid 'n gemeenskapsverantwoordelikheid verteenwoordig wat nie net deur enkele groepe van persone nie, maar deur alle lede van die samelewing aangepak moet word.

'n Ander aspek van die saak, waarna ons nou hier kortliks wil verwys en wat ewe-eens 'n gemeenskapsverantwoordelikheid is, is die voorkoms van padongelukke wat grotendeels aan die gedrag en optrede van voetgangers gewyt kan word. Dit is nie net 'n feit dat 'n baie groot aantal voetgangers elke jaar deur motors beseer word nie, maar dit is ook ontstellend waar dat in stedelike en ander digbeboude gebiede verreweg die meeste ongelukke wat betref voetgangers in verband staan met motors.

'n Interessante studie wat belangrike lig werp op aspekte van dié probleem, is onlangs onderneem deur die Stadspolisiedepartement en die hoofgesondheidsbeampte van die stad New York, in samewerking met die Cornell Mediese Skool. In hierdie ondersoek is in 200 noodlottige gevalle van motorongelukke waarby voetgangers gedood is, die verongeluktes in besonderheid ondersoek. 'n Outopsie is in elke geval uitgevoer. Die volgende is sommige van die insiggewende besonderhede wat aan die lig gekom het:

In meer as driekwart van die noodlottige ongelukke (waar verantwoordelikheid of aandadigheid met 'n redelike mate van sekerheid aan iemand toegeskryf kon word — 147 uit 191) was die voetgangers self verantwoordelik vir die ongeluk deurdat hulle die een of ander veiligheidsregulasie oortree het, bv. deur teen die aanduiding van die verkeersligte die straat oor te steek, deur onverskillig oor die pad te loop, ens. In slegs 10 van die 165 betrokke motors wat ondersoek kon word, is defekte gevind. (Hierdie feit sluit natuurlik nie die rol van die motorbestuurders uit nie.)

'n Ondersoek is ook gedoen na die alkoholinhoud van die bloed en breinweefsels van almal wat binne 24 uur na die ongeluk oorlede is. Van die 104 gevalle wat só ondersoek kon word, is die aanwesigheid van alkohol in die genoemde weefsels gevind in 45 (43%). Hierdie syfer sou waarskynlik nog veel hoër gewees het indien die postmortem ondersoeke vroeër (ten tyde van die ongeluk, byvoorbeeld) gedoen kon word.

Driekwart van die noodlottige gevalle was mans — 'n bevinding wat die vermoede versterk dat alkohol 'n bykomende faktor was. Die meeste slagoffers was in die ouer (50 +) ouderdomsgroep, en daar was ook 'n relatiewe hoë voorkoms by kinders onder die ouderdom van 10. Adolessente en jong volwassenes is betreklik selde betrokke by noodlottige besering van voetgangers deur motors.

In 'n padveiligheidsprogram moet hierdie feite dus deeglik in gedagte gehou word. Om mee te begin, kan daar geen twyfel bestaan dat 'n volgehoue poging tot opvoeding van die publiek in die algemeen en van kinders in die besonder, om verkeersreëls — ook en veral as voetgangers — getrou na te kom, noodsaaklik is nie. Daar is al by geleentheid in al ons grotere stede pogings in hierdie verband aangewend. Dié pogings kan egter slegs suksesvol wees as hulle doelgerig volgehou word. Padveiligheids-

programme in hierdie verband behoort as geïntegreerde en volgehoue ondernemings aangepak te word deur alle skole in samewerking met alle dorps- en stadsowerhede.

Ook is dit ontstellend om die genoemde indirekte bewyse te sien van die vernietigende uitwerking van die misbruik van alkohol. Hierdie feit moet duidelik en helder onder die aandag van die publiek gebring word: nie net dat dit gevaarlik is om 'n motor te bestuur as jy onder die invloed van alkohol is nie, maar ook dat dit onder dié omstandighede gevaarlik is om in 'n publieke straat of pad te loop!

Die soort ondersoek waarna ons hierbo verwys het (wat deur die stadspolisiedepartement van New York onderneem is in samewerking met die ander genoemde instansies), is van die grootste belang omdat dit *'n spesifieke lig* werp op aspekte van 'n vraagstuk wat anders gewoonlik in duisterheid en vae veralgemenings versluier is. As lede van die mediese professie en van die breëre publiek is dit ons plig om hierdie spesifieke kennis toe te pas in ons benadering van die soort van probleem waaroor ons skryf.