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IMPAIRMENT OF ABSORPTION OF ASCORBIC ACID FOLLOWING INGESTION OF ASPIRIN IN GUINEA PIGS

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Abstract—A study was undertaken to investigate the interactions between aspirin and ascorbic acid in guinea pigs. Animals received by gastric intubation either a single dose of radiolabelled ascorbic acid alone or ascorbic acid with aspirin and the exhalation of CO_2 was monitored for 400 min following administration. Animals receiving the vitamin only reached plasma peak levels within 90 min following administration while coadministration of the vitamin with aspirin, not only resulted in lower plasma peak levels, but also delayed their attainment until after 160 min. The bioavailability of ascorbic acid during the first 400 min was reduced by half following simultaneous administration of aspirin. The initial rate of exhalation of CO_2 was decreased by 70% following coadministration of aspirin. These observations indicate that aspirin impairs the gastrointestinal absorption of ascorbic acid in guinea pigs, possibly by interfering with its active transport.

Acetylsalicylic acid (aspirin), a non-narcotic analgesic enjoys extensive use in a number of conditions. The ready availability of the compound leads to consumption of large doses, often simultaneously with other drugs. Interactions of aspirin with other drugs and essential nutrients, such as vitamins, have been reported by a number of workers [1–3].

The interactions between aspirin and ascorbic acid have been the subject of many studies. Administration of therapeutic doses of aspirin to healthy human volunteers decreased the metabolic availability of ascorbate [4–6]. Similarly, rheumatoid arthritic patients ingesting high doses of aspirin exhibited low levels of platelet ascorbic acid [7]. It is evident that such interactions are of clinical importance, especially in people with inadequate or borderline intake of the vitamin.

The exact mechanism of this interaction is not yet clear. *In vitro* studies suggested that the low platelet and leukocyte levels of the vitamin may be due to, at least partly, inhibition of the uptake in the presence of aspirin. However, to our knowledge there has been no report on the possible interactions of the analgesic and the vitamin during gastrointestinal absorption. Such an interaction could be responsible for the low levels of ascorbic acid in leukocytes and platelets following intake of aspirin [4, 6]. In clinical studies where aspirin and ascorbic acid were concurrently administered [5, 6] it was assumed that there was no interaction at gut level although direct evidence was not provided. The present study investigates the effect of aspirin administration on the absorption and metabolism of [^{14}C]ascorbic acid in the guinea pig, as measured by the exhalation of $^{14}CO_2$.

MATERIALS AND METHODS

L-[^{14}C]Ascorbic acid (sp. act. 20 mCi/mmole) was obtained from the Radiochemical Centre (Amersham, U.K.). L-Ascorbic acid and sodium salicylate (soluble aspirin) were purchased from BDH (Poole, U.K.). Dimilume-30 was purchased from Packard Instrument Co. (Reading, U.K.).

Male Dunkin Hartley guinea pigs, weighing 330–420 g (Animal Virus Research Institute, Pirbright, U.K.), were allowed free access to water and to chow diet [RPG Dixon Ltd (Ware, U.K.); ascorbic acid content 1.3 g/kg]. They were randomly divided into two groups, the first group receiving a single oral dose by gastric intubation of ascorbic acid (50 mg/kg) and sodium salicylate (750 mg/kg) in 10% sucrose while animals in the second group received only ascorbic acid and the corresponding volume of 10% sucrose. All animals were also administered orally 6 μCi of L-[^{14}C]ascorbic acid. Individual animals were kept in air-tight metabolic cages (Jencon, Herts, U.K.) which permit the collection of expired air. Animals were allowed a 12-hr acclimatisation period prior to commencement of the experiment. A steady air flow (80 ml/min) was maintained throughout the experiment; the air passed through a soda lime column to remove CO_2. Respiratory CO_2 was trapped in two scintillation vials arranged in series and containing a mixture of ethanolamine:2-ethoxyethanol (3:1) (7.5 ml), 25 M NaOH (0.25 ml) and phenolphthalein indicator which turned colourless when 6.25 mmoles of CO_2 were trapped. Aliquots of the trapping agent were mixed with Dimilume-30 (8 ml) in scintillation vials and the radioactivity was measured using an Ultrabeta LK-1210 scintillation counter.

RESULTS

The exhalation of CO_2 in guinea pigs following an oral administration of ascorbic acid decreased when aspirin was simultaneously administered (Fig. 1). The exhalation rate was markedly inhibited by the analgesic (Table 1) and the cumulative exhalation of CO_2 in the animals receiving this agent in addition

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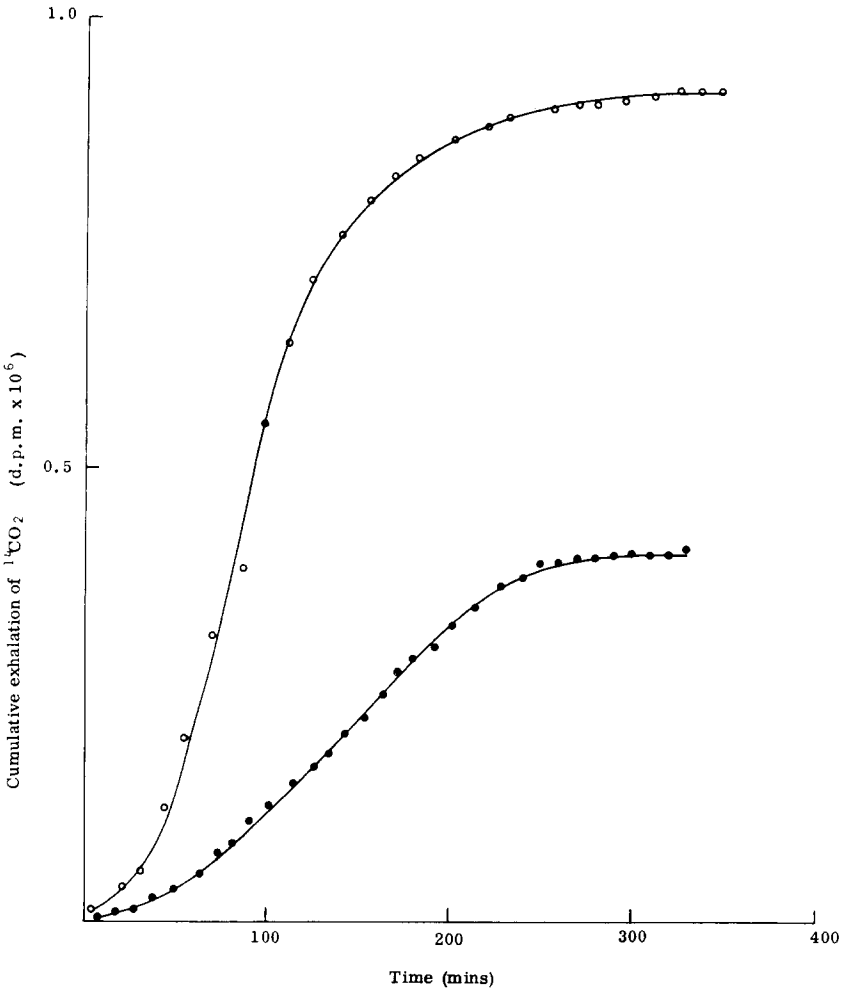

Fig. 1. Effect of aspirin on the cumulative exhalation of CO_2 following ascorbate administration. ○——○, ascorbic acid; ●——●, ascorbic acid + aspirin.

to ascorbic acid was 50% of that observed in animals which received ascorbic acid only.

Ascorbic acid administered alone reached a peak exhalation rate (9.1×10^3 dpm/min) within 90 min following administration (Fig. 2). However, when aspirin was coadministered the peak exhalation rate was markedly decreased (3×10^3 dpm/min) and was achieved much later (Table 1). Determination of the area under the curve during the first 400 min showed that aspirin administration reduced the bioavaila-

Table 1. Effect of sodium salicylate on the $^{14}CO_2$ exhalation following ingestion of L-[^{14}C]ascorbic acid

Parameter	Ascorbic acid	Ascorbic acid + sodium salicylate
Initial rate of exhalation (dpm × 10^3/min)	7.7 ± 1.7 (4)	2.3 ± 0.2 (3)*
Peak exhalation rate (dpm × 10^3/min)	9.1 ± 2.3 (4)	3.0 ± 0.6 (3)*
Time taken to reach peak exhalation rate (min)	87.5 ± 2.5 (4)	157 ± 65 (3)
$AUC_{0-400\,min}$ (dpm × 10^6)	2.2 ± 0.1 (4)	1.1 ± 0.1 (2)*

Results are presented as the mean ± S.D. for the number of determinations shown in parentheses.

AUC = area under the curve.

*$P < 0.005$.

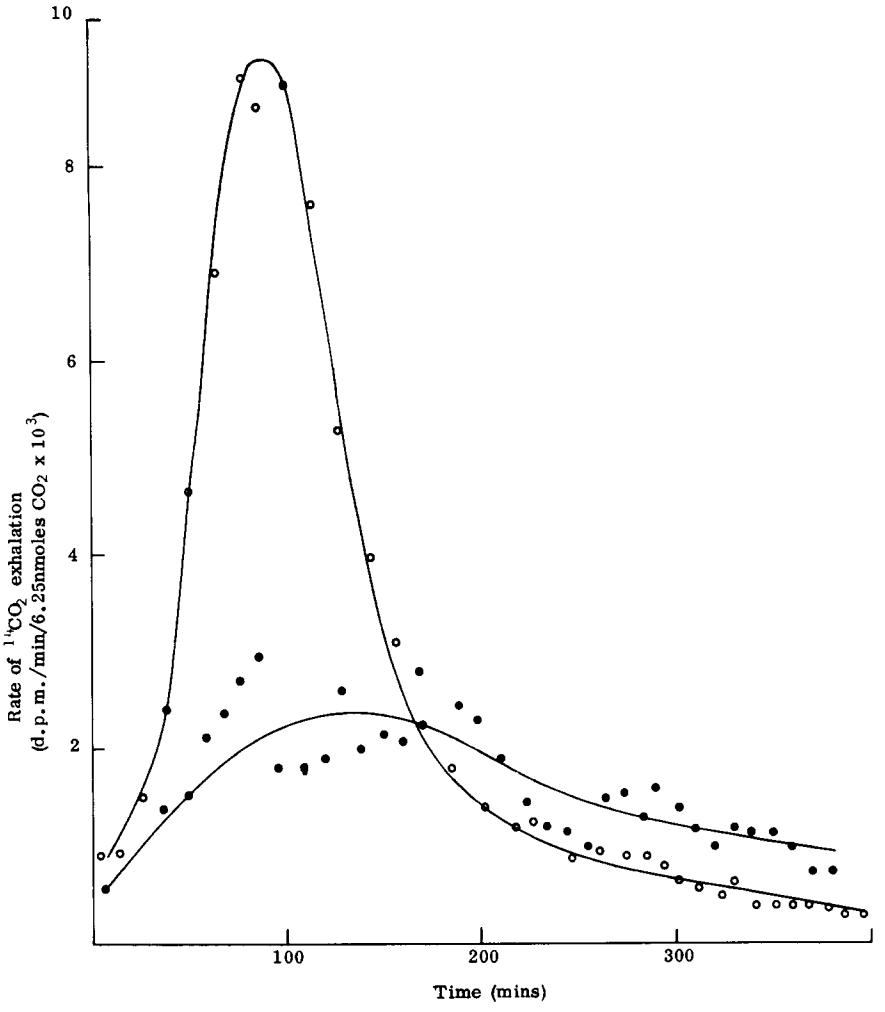

Fig. 2. Effect of aspirin on the rate of exhalation of CO_2 following ascorbate administration. ○——○, ascorbic acid; ●——●, ascorbic acid + aspirin.

bility of ascorbic acid by 50% (Table 1). Urinary excretion of [^{14}C]ascorbate and metabolites during the first 400 min following administration of the vitamin was 2.5 ± 0.9% and 2.0 ± 1.5% of the dose in the absence and presence of aspirin respectively.

During the course of the experiment none of the animals showed any sign of toxicity.

DISCUSSION

In the guinea pig 70% of a dose of ascorbic acid is excreted as CO_2 during the first 10 days following administration, half of which is eliminated during the first day [8, 9]. Exhalation of CO_2 provides, therefore, good means by which the metabolism of ascorbate and its interactions with other agents could be studied.

Following an oral administration of ascorbic acid the peak exhalation rate of CO_2 appeared to occur within 90 min indicating that the vitamin is rapidly absorbed through the gastrointestinal tract (it must be noted that the animals were not starved prior to drug administration). It was of interest that the exhalation rate was markedly decreased, and that the peak exhalation rate was not reached until after more than 155 min, when ascorbic acid was administered concomitantly with aspirin. The fact that aspirin lowers the rate and decreases the extent of absorption of ascorbic acid can be seen by the halving of the bioavailability of the vitamin when aspirin is concurrently administered. It is unlikely that aspirin interferes with the metabolism of ascorbic acid, since a decrease in the rate of CO_2 exhalation following aspirin administration was evident as early as 10 min after the administration of ascorbate when the rate of absorption is much higher than the rate of elimination. Furthermore, the rate of CO_2 exhalation, following completion of absorption and distribution phases, is the same in the animals taking ascorbate alone or ascorbate plus aspirin (Fig. 2). Urinary excretion of ascorbate and its metabolites was unaffected by simultaneous administration of aspirin inidicating that the tissue uptake of the vitamin was not impaired.

In the guinea pig absorption of ascorbic acid through the gastrointestinal tract occurs by active

transport [10]. Since both aspirin and ascorbic acid are weak acids, having similar structures, the possibility that they may compete for the same transport carrier and so impair each other's absorption cannot be excluded [11]. Indeed it has been reported that aspirin depresses the leukocyte uptake of ascorbic acid by inhibiting its active transport [6]. It is very unlikely that passive diffusion of ascorbic acid is important in the guinea pig, as in the rat and hamster [12], since in that case aspirin would facilitate the absorption of the vitamin by decreasing its extent of ionisation.

Aspirin at therapeutic doses has also been reported to impair energy-dependent processes in the gut such as the absorption of glucose and sodium [13], possibly by uncoupling mitochondrial oxidative phosphorylation [14, 15], as evidenced by a decrease in mucosal ATP levels [16, 17]. Since active transport is an energy-dependent process, the deleterious effect of aspirin on mitochondria may also contribute to the impaired absorption of ascorbic acid.

Man, like the guinea pig, is unable to synthesize ascorbic acid and relies on dietary intake; the vitamin is also absorbed in man by an active process [18]. It is, therefore, likely that an interaction with aspirin may also occur in man. Although a single acute dose of aspirin has been employed in this study, similar effects are likely to occur when aspirin is taken as an anti-inflammatory drug, when doses higher than 4 g/day are taken chronically. Prolonged intake of aspirin will result in a deficiency of the vitamin, which in turn will affect the microsomal mixed-function oxidases, the enzymes responsible for the deactivation of xenobiotics, and therefore, alter the sensitivity of patients to drugs [3].

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