Aspartame Pharmacokinetics—The Effect of Ageing


Summary
Aspartame is an intense sweetener which is increasingly used in the UK. It is registered at an acceptable daily intake (ADI) of 40 mg/kg, although there are no previous data relating to the metabolism of aspartame in older people. Twelve young and 12 elderly volunteers each received a single dose of approximately 40 mg/kg of aspartame. Baseline concentrations of phenylalanine (the main metabolite of aspartame) rose after ingestion with a significantly higher maximum concentration (Cmax) (81.3 vs. 63.3 μmol/l, p < 0.01) and area under the plasma concentration–time curve extrapolated to infinity AUC(0-∞) (518.7 vs. 353.5 μmol • h/l, p < 0.01) in the elderly group. The higher concentrations reflected a significant fall in volume of distribution (V) from 2.03 to 1.59 l/kg (p < 0.05) and clearance (CL) from 7.3 to 4.9 ml/min/kg (p < 0.005) in the elderly group. The greater effect on CL than on V resulted in a small but non-significant rise in elimination half life (3.5 to 3.9 hours). The sizes of the differences were modest implying that there is no need on pharmacokinetic grounds for a change in the ADI for older people.

Introduction
Aspartame (N-alpha-aspartylphenylalanine-1-methyl ester) is a 'permitted sweetener' which has a sweetening power 180–200 times that of sucrose. It is manufactured and sold under the brand name Nutra Sweet. There are four intense sweeteners of which saccharin, aspartame and acesulfame-K are licensed in the UK. Cyclamate was withdrawn because of animal toxicity. Aspartame is presently used as an intense sweetener in a range of foods including diet soft drinks, yoghurt, powdered drinks and as a table-top sweetener. One can of diet soft drink contains about 200 mg of aspartame and one pot of diet yoghurt contains about 50 mg [1].

A recent study of intake of sweeteners in the UK [1] documented the current patterns of consumption and predicted that the overall and individual intakes of aspartame will continue to increase. According to this recent report the UK per capita consumption of aspartame is 19.6 mg per day.

Aspartame was registered for use in the United Kingdom in 1983 at an ADI of 40 mg/kg. ADI was originally defined as the daily intake of a chemical which, during an entire lifetime, appears to be without appreciable risk on the basis of all known facts at the time. ADI has been redefined recently as an estimate, by the Joint Expert Committee on Food Additives, of the amount of food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk [2]. The usual way of determining an ADI is to take the 'no observed effect' level in rodents and then divide it by an arbitrary safety factor of 100 which allows for unknown or undefined variables in the extrapolation from animal to man. All food additives licensed in the UK have an ADI agreed by the Ministry of Agriculture, Fisheries and Food (MAFF).

Aspartame is metabolized rapidly in the gut wall to aspartate, phenylalanine and methanol [3], the latter being undetectable in peripheral blood or even in portal blood [4]. Phenylalanine is converted in the liver to tyrosine which is eventually oxidized to carbon dioxide. Both phenylalanine and tyrosine are normal constituents of human plasma. It has been shown that the 1-methyl group is removed from aspartame as a result of pre-systemic metabolism and that the stomach takes no part in the absorption or metabolism of aspartame [5].

Aspartame is completely metabolized by the action of pancreatic alpha-chymotrypsin, an esterase, to yield methanol and L-aspartyl-L-phenylalanine [6]. Within the gut wall, L-aspartyl-L-phenylalanine is cleared by an amidase to yield free phenylalanine which is actively transported through the gut wall into the portal circulation. Further studies support the observation that aspartame is completely hydrolysed in the gut and that little or no aspartame is absorbed intact into the systemic circulation [7, 8]. In children with phenylketonuria, elevated plasma phenylalanine levels are associated with mental retardation. In such children,
plasma phenylalanine levels vary between 1800 and 3000 μmol/l [9].

There are no data relating to these processes in elderly people. The reduction in liver volume associated with ageing [10] would be expected to result in reduced clearance of the metabolites and hence higher serum concentrations. This study was therefore designed to test this hypothesis.

Methods

A pilot study was performed in four volunteers (two elderly and two young) in order to confirm that a dose of 40 mg/kg aspartame was sufficient to enable the pharmacokinetics of the main metabolites to be delineated against the background of physiological concentrations of phenylalanine and tyrosine. Following the protocol for the main study detailed below each was given aspartame and placebo in random order.

In the main study we recruited 12 healthy volunteers aged between 20 and 41 years (six women) and a further 12 aged between 65 and 80 years (six women) after obtaining their informed consent. Young volunteers weighed between 51 and 75 kg with a mean of 66.4 kg, and the elderly volunteers were between 56.5 and 86.5 kg with a mean of 68.6 kg. After a 10-hour fast, each was given approximately 40 mg/kg of aspartame orally as capsules with an aspartame-free glucose drink (200 ml Lucozade) to prevent protein catabolism. The Lucozade drink was given again 2 hours after dosing. Four hours after dosing, a low-protein meal was served (low protein pasta 100 g and Ragu pasta sauce 100 g). Blood samples were taken immediately prior to dosing and frequently over the next 8 hr at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0 and 8.0 hr after dosing. Each blood sample was divided into two aliquots: one fluoride-treated for whole-blood methanol assay and one separated for serum assays of aspartate and phenylalanine.

Pharmacokinetic analysis was performed by modelling the mean of the four phenylalanine concentration–time curves after placebo to derive a modelled background curve. Each individual concentration–time profile following aspartame was background corrected. This process subtracted the background concentrations and constrained the time zero concentration to zero (Figure 3). Finally AUC and Cmax values were derived from each background corrected profile. AUC values were calculated using the linear trapezoidal method and extrapolating the last measured concentration to infinity using the elimination rate constant derived from non-linear optimization of a curve-stripping derived estimate [11].

Tyrosine and phenylalanine in the pilot study were assayed by HPLC with ion-exchange chromatography with coefficients of variations (CV) of 13% at 108 μmol/l for phenylalanine and 11% at 80 μmol/l for tyrosine. As a result of these relatively large CVs, an enzyme diagnostic assay based on the quantaase assay used in phenylketonuria was developed for the main study. The CV for this assay was 3.9% at a concentration...
Table. Mean phenylalanine AUC (μmol.h/l) Cmax (μmol/l), volume of distribution assuming full bioavailability (V) (l/kg), clearance assuming full bioavailability (ml/min/kg) and elimination half life (t½z) (h) values in 12 young and 12 elderly volunteers after dosing with approximately 40 mg/kg body weight of aspartame—statistical comparisons were made using Students’ unpaired t tests with two-tailed tests of significance.

<table>
<thead>
<tr>
<th>AUC</th>
<th>Young</th>
<th>Minimum 216.9</th>
<th>Maximum 497.6</th>
<th>Mean 353.5</th>
<th>SD 94.3</th>
<th>p value &lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>357.0</td>
<td>692.9</td>
<td>518.7</td>
<td>100.0</td>
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<td></td>
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<tr>
<td>Cmax</td>
<td>Young</td>
<td>42.9</td>
<td>80.3</td>
<td>63.3</td>
<td>9.6</td>
<td>&lt;0.01</td>
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<tr>
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<td>45.0</td>
<td>115.2</td>
<td>81.3</td>
<td>18.9</td>
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<tr>
<td>V</td>
<td>Young</td>
<td>1.09</td>
<td>2.90</td>
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<td>Elderly</td>
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<td>2.73</td>
<td>1.59</td>
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<td>CL</td>
<td>Young</td>
<td>5.10</td>
<td>11.36</td>
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<tr>
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<td>6.95</td>
<td>4.87</td>
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<tr>
<td>t½z</td>
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<td>3.5</td>
<td>1.3</td>
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</tr>
<tr>
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<td>6.9</td>
<td>3.9</td>
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</tr>
</tbody>
</table>

of 61.9 μmol/l. Tyrosine was not assayed in the main study. Phenylalanine pharmacokinetic parameters in young and old groups were compared using a two-tailed unpaired t test.

Results

The pilot study demonstrated phenylalanine concentrations well above the background values for phenylalanine in both old and young volunteers. For tyrosine, the values were higher throughout the sampling period other than at baseline but no clear Cmax was discernible. Following placebo, endogenous levels averaged over 8 hours were approximately 68 μmol/l for phenylalanine and 59 μmol/l for tyrosine. Aspartame ingestion substantially increased the amount of phenylalanine and tyrosine to mean levels of 92 μmol/l and 66 μmol/l respectively (Figures 1 and 2). In the main study, mean background corrected AUC(0-infinity) values were higher in the elderly than the young volunteers for phenylalanine (518.7 vs. 353.5 μmol.h/l, p < 0.01). Similarly, the mean background corrected Cmax for phenylalanine was significantly higher in the elderly versus young volunteers (81.3 vs. 63.3 μmol/l, p < 0.01) (Table and Figure 3). These differences persisted even when the values were corrected for absolute dose. Clearance (CL) and volume of distribution (V) were significantly lower in the elderly group (Table). As CL fell slightly more than V, elimination half life (t½z) showed a non-significant rise in the elderly group.

Discussion

This is the first report on age-associated variation in the pharmacokinetics of the metabolites of aspartame. We have demonstrated a significantly increased AUC and Cmax of phenylalanine, the main metabolite of aspartame, after weight-corrected dosing of the parent drug. Findings of Stegink et al. [3] and Burns et al. [12] were similar to those in the young volunteers in our study.

The explanation for the fall in CL in healthy elderly volunteers almost certainly relates to the fall in liver volume associated with ageing [10]. The effect of the change in body composition with ageing would be expected to increase V in elderly volunteers as phenylalanine is lipid soluble (mean V 1.59 l/kg). It does not bind significantly to plasma proteins which in other situations might be an explanation for a fall in V. As t½z is a function of the ratio of V : CL, the slight rise in t½z reflects the greater fall in CL than V. In common with other aminoacids, phenylalanine tissue penetration is by a combination of mechanisms including passive diffusion, facilitated diffusion and active uptake. If active uptake were to be partially saturated at the time of the higher peak concentrations seen in the elderly volunteers, this would reduce the calculated V and is hence a possible explanation for our findings, although we have no data to support the hypothesis. These very modest differences give no concern on pharmacokinetic grounds over the ADI of aspartame in elderly people.

Acknowledgement

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References

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