Comparison of effects of calcium carbasalate and aspirin on gastroduodenal mucosal damage in human volunteers

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Abstract

Calcium carbasalate is a therapeutically active salicylate which seems to cause less gastroduodenal mucosal damage than aspirin in laboratory animals. This endoscopist-blinded, randomised, cross over trial aimed to compare acute gastric mucosal damage in 20 healthy volunteers treated with acetyl salicylic acid (ASA) (650 mg three times daily) and effervescent calcium carbasalate (ECC) (826·8 mg three times daily) bioequivalent to 650 mg ASA over a five day period. Endoscopy was performed immediately before treatment and on day 5 of each treatment. Serum salicylate, thromboxane B_2, and gastric mucosal prostaglandin E_2 (PGE_2) concentrations were measured after endoscopy. ECC caused fewer gastric mucosal erosions than ASA. The total number of gastric erosions was 23·8 (16·1) in the ASA treated subjects compared with 9·1 (8·7) in ECC treated subjects (p=0·004). Differences between ASA and ECC were significant for both the gastric antrum and body, and for both haemorrhagic and non-haemorrhagic erosions. The mean gastric body Lanza score for mucosal damage was lower after ECC than ASA (p=0·003). The visual analogue score for gastric body damage was lower for ECC (16·9 mm (15·9)) than for ASA (32·7 mm (20·8)), p=0·008. Serum salicylate concentrations were similar after both preparations (ASA: 66 (23) mg/l, *versus* ECC: 58 (17) mg/l, NS). Serum thromboxane B_2 was similarly reduced using both preparations – 97·2 (3·5)% inhibition with ASA, 95·2 (5·5)% inhibition with calcium carbasalate (NS). Suppression of gastric mucosal PGE_2 synthesis was similar with both preparations (ASA: 83·4 (17·1)%; ECC 84·3 (12·9)%; NS). It is concluded that ECC causes significantly less gastroduodenal mucosal damage than ASA administered at bioequivalent doses as judged by serum salicylate, serum thromboxane, and mucosal PGE_2 values. ECC may therefore be a less harmful alternative treatment to plain ASA.

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Acetyl salicylic acid (ASA) causes acute gastroduodenal mucosal injury, resulting in substantial morbidity and mortality from peptic ulcer disease. Effervescent calcium carbasalate (ECC) is a calcium urea chelate of two aspirin molecules, formed by replacing the two molecules of water in crystalline calcium acetyl salicylate by a molecule of urea. It forms a stable and very soluble complex. In solution, the complex immediately releases aspirin in the form of acetyl salicylate ion. When administered orally, the acetyl salicylate is readily absorbed and has similar analgesic, antipyretic, and anti-inflammatory properties to aspirin. Studies using intramucosal potential difference and gastrointestinal bleeding have suggested that ECC may be less damaging to the human gastrointestinal tract.[1-4]

We now report a direct comparison of gastroduodenal injury, assessed endoscopically, caused by plain ASA for five days and effervescent calcium carbasalate (826·8 mg three times daily, equivalent to 650 mg ASA three times daily for five days).

Patients and methods

This was a randomised, endoscopist-blind, cross over trial comparing the effects of effervescent calcium carbasalate (ECC) and plain ASA on gastroduodenal mucosal injury in healthy volunteers. Healthy volunteers of either sex, aged between 18 and 45, within 15% of their desirable weight (according to Metropolitan Life tables), were recruited. After giving written informed consent, subjects were screened to enter this study.

Subjects underwent a medical examination with haematological and biochemical screening and a screening endoscopy before the start of the study. The main exclusion criteria included asthma, peptic ulcer disease, aspirin intolerance, and the presence of more than three erosions at screening endoscopy.

Volunteers were instructed to refrain from drugs (except oral contraceptives), alcohol, and spicy food during the study. They were randomised to receive either 325 mg plain ASA (Aspirin, Bayer) or ECC containing 413 mg acetyl salicylate (Redupsan, UPSA, Rueil Malmaison, France) first. During the active treatment period, subjects were instructed to take two tablets 20 minutes before each meal (breakfast, lunch, and dinner) for four days and one dose on the fifth day. There was a wash out period of 16 to 23 days between active treatments.

Before treatment and on day 5, subjects underwent evaluation of symptoms and adverse events, endoscopic evaluation, and had blood

TABLE I *Modified Lanza scale*

Score	Endoscopic appearances
0	Normal mucosa
1	Mucosal erythema
1	1–5 Erosions
3	6–10 Erosions
4	>10 Erosions or an ulcer

samples taken from serum salicylate and thromboxane B_2 (TxB$_2$) measurement. Endoscopy was performed without sedation. The number of erosions (both haemorrhagic and non-haemorrhagic), intramucosal haemorrhages, and superficial and deep ulcers in the oesophagus, stomach, and duodenum were counted. These data were used to derive a modified Lanza score of mucosal damage (Table I). A visual analogue score (100 mm) of mucosal damage was also used to evaluate gastric antrum, body, and duodenal damage. Endoscopic biopsy was performed in the gastric body to determine PGE$_2$ synthesis. After withdrawal of the endoscope, blood was taken for estimation of serum salicylate by high performance liquid chromatography (HPLC). Serum TxB$_2$ and mucosal prostaglandin E$_2$ (PGE$_2$) were assayed as previously described.[5][6] Briefly, mucosal biopsy specimens were washed in 0·15 ml of Tris-saline and vortexed in 500 μl of Tris-saline for one minute at room temperature. The biopsy specimens were then removed and washed and the supernatant stored at −70°C until assayed. PGE$_2$ was measured in unextracted supernatant using a validated specific radioimmunoassay (RIA), and expressed as pg/mg wet weight of gastric mucosa. The serum TxB$_2$ concentration was measured in separated serum using RIA.

STATISTICAL METHODS

From previous data, we estimated an average total number of erosions with aspirin of 11·2 and aimed for the power to detect reduction of mucosal damage by two erosions (29% reduction $\alpha=0·05$, $1-\beta=0·9$). As a result of sample size calculation in log transformed values this led to 20 subjects being recruited to complete the study.

Statistical analysis was done using the *SAS* and the *Statexact* packages. All tests were two tailed; p values below 0·05 were considered

significant. The results were expressed as mean (SD) (as well as mean and interquartile range (IQR) for efficacy criteria) for quantitative parameters and frequencies and percentages for qualitative parameters. Data regarding the Lanza scale are expressed as median (IQR). The two randomised groups were compared for demographic parameters using the Pearson's χ^2 test for qualitative parameters and the Student's t test for quantitative parameters.

The efficacy analysis was performed in three steps. Firstly, the presence of residual effects was investigated using the paired sample t test for quantitative parameters and the initial assessments at the first visit and the third visit (baseline evaluations before each sequence under active treatment). Secondly, within treatment effects were tested using the same tests to compare initial and final assessment within each treatment, pooling the subjects of the two sequences. Thirdly, the two treatments were compared using a two way analysis of variance model (testing treatments effect, sequence effect and sequence by treatment interaction) for quantitative parameters and a modified χ^2 test (Cochran Mantel-Haenszel test) to compare the frequencies of qualitative parameters adjusting for the sequence.

Results

PATIENT POPULATION

Twenty two volunteers were screened to enter the study. One subject was not included in the study because of the presence of a baseline biochemical abnormality (raised serum creatinine) and did not receive either treatment. One other subject who had been randomised to plain ASA dropped out before the end of the first treatment period because she was unwilling to undergo further endoscopy. She did not complain of any symptom while taking the treatment and reported no adverse event.

Thus 20 subjects (16 men and 4 women, aged 23·95 (3·6) years (range 19–35), and weight 73 kg (8)) completed the entire study and were evaluated. Eleven subjects received ASA as the first treatment and ECC as the second treatment; nine subjects received ECC as the first treatment and ASA as the second treatment.

COMPARISON OF EFFECTS OF ASA AND ECC ON GASTRIC MUCOSAL DAMAGE

There was no difference in the number of erosions at baseline in the two groups. There was no carry over from one treatment period to the next. No effect on oesophageal mucosa in terms of erythema or erosions was observed.

As previously observed, ASA caused a highly significant and noticeable increase in the total number of gastric erosions and ulcers (haemorrhagic and non-haemorrhagic) in the stomach as a whole, from 0 to 23·8 (16·1) (p<0·005) (Table II). This increase was seen in both the body (from 0 to 12·4 (9·7) (p=0·0001) and the antrum (from 0·1 to 11·4 (9·4)) (p=0·0001) (Table II). For ECC, the total number of

TABLE II *Comparison of gastroduodenal damage associated with five days' treatment with acetyl salicylic acid (ASA) or effervescent calcium carbasatate (ECC) (values mean (SD))*

	Total no of erosions		
	ASA	ECC	p Value
Gastric body:			
Total erosions and ulcers	12·4 (9·7)	5·0 (7·3)	0·005
Haemorrhagic erosions	11·8 (9·6)	4·6 (6·9)	0·004
Non-haemorrhagic erosions	0·7 (1·5)	0·4 (1·0)	
Lanza score (IQR)	3 (2–4)	2 (0–2)	0·003
VAS (mm)	32·7 (20·8)	16·9 (15·9)	0·008
Gastric antrum:			
Total erosions and ulcers	11·4 (9·4)	4·1 (4·1)	0·002
Haemorrhagic erosions	5·7 (6·9)	2·2 (2·7)	0·006
Non-haemorrhagic erosions	5·5 (5·8)	1·9 (3·0)	0·01
Lanza score	3·5 (3–4)	2 (0·5–2)	0·0006
VAS (mm)	36·9 (19·3)	17·9 (15·7)	0·002
Duodenal bulb:			
Total erosions and ulcers	3·6 (4·9)	2·1 (4·4)	NS
Non-haemorrhagic erosions	0·4 (0·8)	0·4 (1·4)	NS
Haemorrhagic erosions	3·2 (4·7)	1·6 (4·2)	NS
Lanza score (IQR)	1·5 (1–2·5)	0·5 (0–2)	NS
VAS (mm)	21·3 (23·9)	12·7 (22·9)	NS
Gastric body+antrum (pooled):			
Total erosions and ulcers	23·8 (16·1)	9·1 (8·7)	0·004
Haemorrhagic erosions	17·5 (14·3)	6·8 (7·2)	0·007
Non-harmorhagic	6·2 (6·3)	2·3 (3·4)	0·02
Gastroduodenal (pooled):			
Total erosions and ulcers	23·7 (17·9)	11·2 (10·0)	0·009
Haemorrhagic erosions	17·8 (14·2)	7·2 (7·4)	0·008
Non-haemorrhagic erosions	9·4 (9·4)	4·0 (5·5)	0·04

VAS=visual analogue scale.

TABLE III *Comparison of effects of acetyl salicylic acid (ASA) and effervescent calcium carbasatate (ECC) on prostaglandin E_2 (PGE$_2$) and thromboxane (TxB$_2$) concentrations*

	ASA	ECC	p Value
Day 5 serum salicylate (mg/l)	66 (23)	58 (17)	NS
Day 5 serum TxB$_2$ (pg/ml)	357 (376)	220 (55)	NS
Inhibition of serum TxB$_2$	97·2%	95·2%	NS
Inhibition of gastric mucosal PGE$_2$	83·4 (17·1)%	84·3 (12·9)%	NS

gastric erosions and ulcers increased from 0 to 9·1 (8·7) for the stomach as a whole (p=0·00001). These increases were seen in both body (0 to 5·0 (7·3), p=0·0001) and the antrum (0 to 4·1) (4·1), p=0·0001) (Table II). The total number of erosions was significantly lower with ECC than ASA whether the whole stomach (p=0·004), the body (p=0·005), or the antrum (p=0·002) was considered (Table II). Most of the gastric erosions observed were haemorrhagic. There were significantly fewer haemorrhagic erosions with ECC than with ASA in the antrum (p=0·006), in the body (p=0·004), and in the stomach as a whole (p=0·007). Antral ulcers were observed in three subjects (one deep, two superficial) while receiving ASA; all had a negative CLO test (Delta West, Perth, Western Australia) suggesting that they were *Helicobacter pylori* negative. No gastric ulcers were seen in the subjects while receiving ECC.

When data were translated into Lanza scores for the stomach, there were significant differences between the two treatments (p=0·003 for gastric body and 0·0006 for antrum) (Table II). Visual analogue scores for gastric body and antrum mucosal damage were also significantly lower after treatment with ECC (16·9 (15·9) and 17·9 (15·7) respectively) than with ASA (32·7 (20·8) and 36·9 (19·3) respectively); p=0·008 and p=0·002 respectively.

EFFECTS OF ASA AND ECC ON DUODENAL MUCOSA
The damage noted in the duodenal bulb was less severe than in the stomach. ASA increased the total number of erosions in the duodenal bulb from 0·05 (0) to 3·6 (4·9) (p=0·001). This was accompanied by a deterioration in the Lanza score from 0 to 1·5 (IQR 1–2·5) (p=0·0003) and the visual analogue score from 0·65 to 21·30 (23·9) mm (p=0·001) (Table II). The numbers of both non-haemorrhagic erosions (0·04 (0·8)) (p=0·002) and haemorrhagic erosions (0 to 3·2 (4·7)) (p=0·04) were increased.

The administration of ECC induced a small but significant (p=0·05) increase in the total number of erosions from 0 to 2·1 (4·4), a worsening of the Lanza score (0 to 0·5 (IQR 0–2) (p=0·002), and an increase in the number of non-haemorrhagic erosions in the duodenum bulb (Table II). With ECC there was no significant increase in haemorrhagic erosions in the duodenal bulb, and there was no significant deterioration in any criteria in the second part of the duodenum (data not shown). Differences in mucosal damage between ASA and ECC in the duodenum did not achieve statistical significance.

When whole stomach and duodenum data

were pooled there was a significant difference in favour of ECC for the total number of erosions (p=0·01), haemorrhagic erosions (p=0·008), non-haemorrhagic erosions (p=0·04), and the total number of erosions and ulcers (p=0·009). One subject developed a superficial ulcer in the duodenal bulb while being treated with ASA and ECC but this was not associated with *H pylori*.

EFFECTS OF ASA AND ECC ON SERUM SALICYLATE, TxB$_2$ AND PGE$_2$ VALUES
The mean serum salicylate concentration measured on day 5 with each treatment was available in 19 subjects with ASA and 18 subjects with ECC. Serum salicylate values measured after treatment with ASA and ECC were similar (66 (23) mg/l *versus* 58 (17) mg/l, NS): Table III. There was a significant suppression in the mean serum TxB$_2$ level after five days treatment with both ASA (30873·75 (31686·05) pg/ml to 375·25 (376·42); p=0·002) and ECC (24238·67 (33270·99) to 220·40 (55·26) pg/ml; p=0·014); the percentages of suppression from day 1 were 97·2% and 95·2% respectively. There was no significant difference between the two treatments for this criterion (Table III). Both treatments also caused significantly reduced gastric mucosal synthesis of PGE$_2$ (Table III).

ADVERSE EVENTS
Eleven subjects reported at least one adverse event while taking ASA, compared with nine subjects while taking ECC. Ten subjects taking ASA experienced indigestion compared with seven taking ECC. Nausea was reported in three subjects on ASA and in two on ECC. Heartburn was reported in two subjects on ASA and in one on ECC. Vomiting was noted in one subject with each drug, and anorexia in one subject while taking ASA. Adverse reactions were graded as mild except for two patients on ASA and one on ECC in whom they were considered moderate. There was no significant difference between the two drugs in this regard. Three subjects receiving ASA developed gastric antral ulceration. In all cases, ulceration healed spontaneously after stopping treatment. No gastric ulcers developed in subjects receiving ECC. One subject developed a superficial duodenal bulb ulceration with both treatments.

Discussion
In this study, ASA and ECC had similar activity as judged by similar serum salicylate concentrations and inhibition of serum TxB$_2$ and gastric mucosal PGE$_2$. Despite this, ECC caused significantly less acute gastric mucosal injury in subjects compared with ASA. In addition, three subjects developed gastric ulceration while taking ASA compared with none taking ECC. These differences persisted when subgroups with erosions classified according to whether they were of haemorrhagic or non-haemorrhagic appearance and whether they

were seen in both the body and the antrum of stomach. There were relatively few erosions in the duodenum but there was a consistent trend towards less damage when subjects received ECC compared with ASA.

These data suggest that ASA and ECC are therapeutically equivalent but that ECC causes less acute gastric injury as assessed by the serum salicylate concentration, inhibition of serum TxB_2 values, and inhibition of mucosal PGE_2 synthesis. If the differences were to persist with longer term ingestion, this would suggest that ECC is less ulcerogenic with chronic use. During the study no gastric ulcers developed in subjects taking ECC, compared with three ulcers with ASA. Our study evaluated relatively high doses of both drugs. ASA is used at lower doses for cardiovascular prophylaxis but it is known that even doses as low as 75 mg/d are associated with easily detectable gastric mucosal injury. If the differences between ASA and ECC were also seen at lower doses, ECC might prove to be a more appropriate agent for cardiovascular prophylaxis. Data emerging from epidemiological studies suggest a 40 to 80% increase in the incidence of bleeding peptic ulcer in patients taking aspirin as cardiovascular prophylaxis compared with placebo.[7]

Our data do not identify the mechanism by which ECC is less injurious than ASA.

Whether the reduction in mucosal damage observed is a result of buffering of salicylate by urea in ECC or of cytoprotective action of ECC is not known. Other possibilities are that aspirin is released from the complex only very slowly so that exposure of the gastric mucosa is effectively limited. However, ECC caused less mucosal damage in the presence of similar levels of inhibition of mucosal PGE_2 synthesis with each compound.

In summary, ECC in doses therapeutically equivalent to ASA in terms of inhibition of serum and mucosal eicosanoid synthesis, caused less gastric mucosal damage than ASA.

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