Absorption kinetics of acetylsalicylic acid in gastrectomized patients

Carmen Hurtado*, Carlos Acevedo, Catalina Domecq, Patricio Burdiles*, Atila Csendes* and Aquiles Arancibia

*Departamento de Ciencias y Tecnologia Farmacéuticas, Facultad de Ciencias Quimicas y Farmacéuticas, Universidad de Chile, and *Centro de Gastroenterologia, Departamento de Medicina y de Cirugia, Hospital Clinico de la Universidad de Chile, Santiago, Chile*

Acetylsalicylic acid (ASA) is one of the oldest and most widely used medicinal agents today and its spectrum of therapeutic use is continually widening. Although many other drugs have been introduced during the last few years, ASA remains in a prominent position as the standard analgesic, antipyretic and anti-inflammatory drug of choice [1, 2].

Gastrectomy consists of a partial or total surgical resection of the stomach, and the continuity of intestinal transit is re-established by means of the anastomosis of the remainder of the stomach with a gastro-duodenostomy (anastomosis Billroth Type I) or by a gastro-jejunostomy (Billroth Type II). When total gastrectomy is performed the intestinal transit continuity is re-established by directly connecting the esophagus with the jejunum (esophagus-jejunostomy) [3].

Orally administered ASA is rapidly and usually completely absorbed from the gastrointestinal tract. Absorption occurs by passive diffusion of unionized lipophilic molecules, partially from the stomach but mainly from the upper small intestine [4].

Gastrointestinal pH has a major influence on the rate of absorption of ASA by the two different mechanisms. At first low pH in the stomach provides optimum conditions for the absorption of undissociated ASA molecules. Then, as pH rises in the small intestine, the dissolution rate of ASA solid particles increases and is maximal at pH 8 [4].

In Chile a large number of patients have undergone gastrectomy because of gastroduodenal disease. A clearer understanding of ASA absorption kinetics is therefore of great importance for the establishment of a safe and effective dose regimen for both acute and long term therapy of gastrectomized patients as well as subjects with normal gastrointestinal function [5].

Patients and methods: Twenty-two subjects were studied, 15 of them having undergone gastrectomy at least 2 months prior to the experiment. Five patients had undergone Billroth I (B I), five patients had Billroth II (B II) and five had undergone total gastrectomy. The patients ages ranged from 31 to 62 years (mean 47.8 ± 8.9 years) and their weights varied from 47 to 74 kg (mean 59.1 ± 8.0 kg). Seven healthy volunteers, six males and one female, whose ages ranged from 21 to 50 years (mean 34.0 ± 11.8 years) and whose weights varied from 56 to 70 kg (mean 61.9 ± 4.9 kg) constituted the control group. Written consent was obtained from all the subjects. A medical history was taken and laboratory tests to assess hepatic and renal functions (serum alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin and creatinine) were carried out prior to the study. The weight/size ratio of both groups was in the normal range [6].

A 500 mg aspirin (Bayer) tablet was allowed to disintegrate and was suspended in 15 ml of water and administered to the subjects with an additional 50 ml of water. Blood samples were drawn before drug administration and at 15, 30, 45, 60 and 90 min and 2, 4, 6 and 8 h thereafter. The drug was administered at 08:00 after an overnight fast. Fasting was continued for the first 4 h after the drug administration, then the subjects received a light meal consisting of one sandwich and a cup of plain tea.

Table 1: Laboratory test results of normal volunteers and gastrectomized patients

	Total bilirubinemia (≤ 1 mg%)[a]	Aspartate aminotransferase (≤ 18 IU/l)[a]	Alanine aminotransferase (≤ 22 IU/l)[a]	Alkaline phosphatase (20–48 IU/l)[a]	Serum creatinine (≤ 1.2 mg/dl)[a]
Healthy controls					
H.M.	1.1	14	5	35	1.0
S.P.	0.3	15	13	40	0.7
R.P.	0.4	20	8	43	1.0
J.T.	0.6	20	40	33	1.2
O.N.	0.6	18	14	41	1.0
J.M.	0.5	16	12	40	1.0
J.V.	0.7	9	2	50	0.9
$\bar{X}$	0.6 ± 0.26	16 ± 3.87	13 ± 12.5	40 ± 5.5	0.97 ± 0.15
Gastrectomized patients					
R.P.	0.7	12	13	55	0.7
M.G.	0.5	16	13	53	1.3
F.Y.	1.3	45	36	55	0.8
H.M.	0.6	33	23	60	0.9
E.H.	0.5	28	50	42	0.9
E.P.	0.5	12	9	38	0.8
G.E.	1.2	13	12	43	0.7
I.M.	0.7	9	8	33	1.1
C.B.	0.5	16	13	42	1.1
E.E.	0.3	30	11	38	1.3
S.P.	0.3	13	11	49	0.9
M.I.	0.4	11	9	44	0.7
O.J.	1.5	24	30	23	0.7
R.O.	1.0	17	19	50	1.0
R.C.	0.5	11	2	38	0.6
$\bar{X}$	0.7 ± 0.37	19 ± 10.4	17 ± 12.6	44.2 ± 9.7	0.9 ± 0.22

[a]*Normal range in parentheses.*

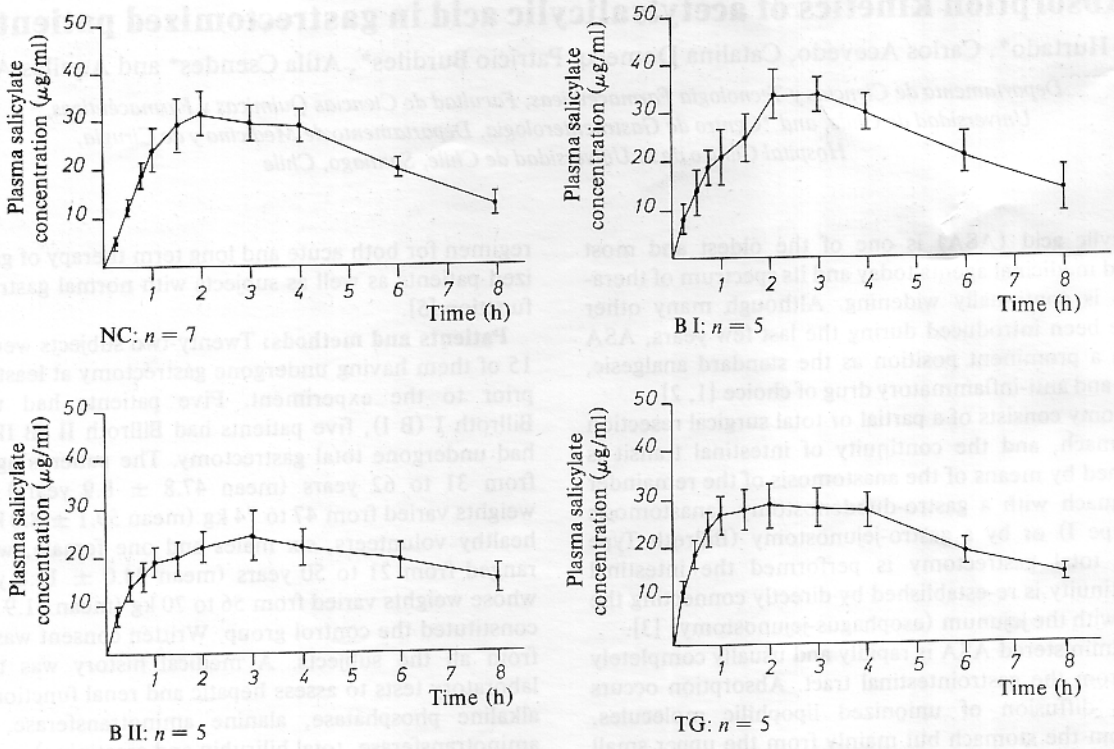

Figure 1: Plasma salicylate concentration (μg/ml), (means ± SEM) vs time (hours) in normal control (N.C.), Billroth I (B I), Billroth II (B II) and total gastrectomy (TG) patients.

Serum salicylate concentrations were measured by spectrofluorometry using the method reported by Chirigos and Udenfriend [7].

The pharmacokinetic parameters were calculated according to a one compartment model using the S.A.S. computer program [8]. Elimination rate constant (K), absorption rate constant (K_a), elimination half life ($t_{½}$), observed maximum serum concentrations (C_{max}) and time to reach this concentration (T_{max}), and finally area under the serum concentration time curve (AUC), were determined by classical pharmacokinetic techniques [9, 10].

Analysis of variance (ANOVA) followed by Tukey test were employed to assess the differences between the groups [11], the criterion of significance was $p < 0.05$.

Results and discussion: Results of the laboratory tests were within normal limits for most subjects (Table 1). Even though abnormal values were seen in some subjects, those values were not indicative of renal and/or hepatic failure. The average salicylate serum levels as a function of time after administration of a single dose of ASA for the four groups are shown in Figure 1. It can be seen that healthy volunteers, B I and total gastrectomy patients presented very similar concentration profiles whilst B II patients showed important differences.

Table 2 summarizes the pharmacokinetic parameters. No statistically significant differences in the elimination parameters, K and $t_{½}$, were found between different groups. B I patients presented the highest values of C_{max} and AUC, 26.8 ± 8.9 μg/ml and 11.32 ± 4.34 μg $ml^{-1}min^{-1}$, respectively. The values of C_{max} decreased in the other groups in the following order: healthy volunteers, total gastrectomized patients and B II patients. A similar feature was observed with respect to AUC values, except that the order was reversed for healthy volunteers and total gastrectomized patients. However, for both parameters the differences were not statistically significant. The absorption process was apparently delayed in B II patients as suggested by the value of T_{max}, which was significantly longer than normal subjects.

It was thought that total gastrectomy would produce marked alterations in the absorption pharmacokinetics parameters. However, these results indicate that there are no significant differences compared with healthy volunteers. It seems that esophagus-jejunostomy produces both a reduction in the intestinal transit rate and a higher pH which favours absorption. These two factors would overlay the effect of a smaller available absorption surface.

In the case of patients with the Billroth I operation, partial resection of stomach decreases the acidity of the gastric contents which would result in increased solubility and better absorption. This is in agreement with the results reported by Prescott *et al.* [12] who found that ASA absorption was increased in patients with achlorhydria. On the other hand, this type of resection speeds up gastric emptying allowing the drug to reach the intestine more promptly, where favourable

Table 2: Pharmacokinetic parameters of salicylate in healthy volunteers and patients with different gastrectomies after a single oral dose of aspirin (means ± SD)

Subjects	*n*	K_a (min^{-1})	K (min^{-1})	AUC (μg $ml^{-1}min^{-1}$)	$C_{max\ obs}$ (μg/ml)	T_{max} (min)	$t_{½}$ (min)
N	7	0.0152 ± 0.0033	0.0035 ± 0.0009	10419.3 ± 3324.2	34.6 ± 10.2	128.7 ± 15.1*	210.2 ± 52.0
B I	5	0.0156 ± 0.0031	0.0032 ± 0.0014	11316.6 ± 4338.8	36.3 ± 8.6	135.5 ± 33.2	249.5 ± 110.1
B II	5	0.0113 ± 0.0068	0.0021 ± 0.0018	9273.5 ± 2909.0	26.8 ± 9.9	243.2 ± 122.4*	538.7 ± 303.2
TG	5	0.0149 ± 0.0024	0.0026 ± 0.0014	10954.9 ± 2683.9	30.0 ± 8.6	149.8 ± 28.9	370.6 ± 266.3

*N = Normal controls, B I = Billroth I, B II = Billroth II, TG = Total gastrectomy. *p < 0.05.*

conditions for absorption exist. This could be the reason why T_{max} shows a tendency to be shorter, and C_{max}, AUC and K_a tend to be larger than in normal subjects, although differences were not statistically significant.

B II patients presented a T_{max} value significantly greater than normal patients. In addition, C_{max} and the AUC tended to be lower, although not significantly. In these patients, the gastro-jejunostomy performed results in a bypass of the duodenum, a very efficient site of absorption. In addition, and probably most important, almost all these patients also had truncal vagotomy which would result in a delay in gastric emptying and, consequently, a longer time for the drug to reach the jejunum, which would be the main site of absorption in these patients. On the other hand, intestinal motility is enhanced in patients with B II which tends to shorten the time of contact of the drug with the absorption surface.

Our results are partially in agreement with those reported by Mineshita [5] in a similar study performed in the same type of patients. He reported that there was a tendency for T_{max} of normal subjects to be shorter than that of gastrectomized subjects but no statistically significant differences were found between them.

Mean elimination half life was apparently longer in all groups of patients, particularly B II patients, when compared with normal subjects, but the differences did not reach statistical significance. It is probable that the half life values reported here could be biased. In fact, elimination rate constants were calculated using the concentration data at 4.6 and 8 h, and it is possible that the absorption process, which tends to be delayed in gastrectomized patients, may not have finished at these times. This would increase the half life. A modification of the protocol would be necessary in order to avoid interference of the absorption process in the elimination half life determination.

1. Kadar, D. (1985) in *Principles of Medical Pharmacology*, 4th edition, (Kalant, H., Roschlau, W.H.E. and Sellers, E.M., eds), pp. 383-398, Department of Pharmacology, Faculty of Medicine, University of Toronto, Canada
2. Shearn, M.A. (1986) in *Basic and Clinical Pharmacology*, 3rd edition, (Bertram, G. and Katzung, A., eds), pp. 393-406, Appleton Lange, California
3. Thompson, J.C. (1980) in *Tratado de Patologia Quirúrgica*, 11th edition, (Sabiston, D.C., ed.), pp. 869-911, Interamericana, Mexico
4. Clissold, S. (1986) *Drugs*, **32**, (Suppl. 4), 8-26
5. Mineshita, S. (1983) *Br. J. Clin. Pharmacol.*, **16**, 756-757
6. Publicación Docente (1977) in *Tablas de peso aceptable para adultos*, (Departamento de Nutrición, ed.), pp. 1025-1077, Facultad de Medicina, Universidad de Chile, Chile
7. Chirigos, M.A. and Udenfriend, S. (1959) *J. Lab. Clin. Med.*, **54**, 769-772
8. S.A.S. User's Guide (1982) *Statistic Regression: The NLIN Procedure*, S.A.S. Inc., Cary, N.C.
9. Gibaldi, M. and Perrier, D. (1982) *Pharmacokinetics*, Marcel Dekker, Basel
10. Arancibia, A. (1981) in *Introducción a la Biofarmacia y Farmacocinética*, in *Farmacotecnia, Teórica y Práctica*, (Helman, J., ed.), pp. 2485-2538, Compañia Editorial Continental S.A., México
11. Zar, J.H. (1974) in *Biostatistical Analysis*, pp. 153-162, Prentice-Hall Inc., USA
12. Prescott, L.F., Pottage, A. and Nimmo, J. (1974) *J. Pharm. Pharmacol.*, **26**, 144-145

Reprint requests to: Professor A. Arancibia, Departamento de Ciencias y Tecnologia Farmacéutica, Facultad de Ciencias Quimicas y Farmacéuticas de la Universidad de Chile, Santiago de Chile, Chile.