

Minimal dose of a stimulus for maximal pepsin secretion

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Summary

Dose-response curves were obtained with subcutaneous histamine acid phosphate (HAP) in twenty-two subjects, intravenous HAP in fifteen subjects, subcutaneous pentagastrin in fourteen subjects and intravenous pentagastrin in twelve subjects in order to determine the minimal doses of these stimuli for maximal pepsin secretion.

The minimal doses for maximal pepsin secretion were 2.8 mg HAP on SHT, 1.2 mg/hr HAP on IHT, 300 µg pentagastrin on SPT and 100 µg/hr pentagastrin on IPT.

FROM dose-response curves, the minimal doses for maximal acid secretion were reported for subcutaneous (Kay, 1953) or intravenous (Lawrie, Smith & Forrest, 1964) histamine acid phosphate (HAP) and subcutaneous (Makhlof, McManus & Card, 1966) or intravenous (Konturek & Lankosz, 1967) pentagastrin (ICI 50123). However, similar dose-response curves to determine the minimal dose of a stimulus for maximal pepsin secretion are not reported. In various studies, the doses of different stimuli which had caused a maximal acid secretion were administered to stimulate maximal pepsin secretion, on the assumption that parietal and chief cells have some definite relationship both in health and disease in all individuals.

The object of this study was to perform dose-response curves with different stimuli with a view to determine the minimal doses for maximal pepsin secretion.

Materials and methods

Dose response curves were performed with subcutaneous HAP in doses of 1.6, 2.0, 2.4, 2.8 and 3.2 mg in twenty-three male subjects (eleven control and twelve duodenal ulcer), with intravenous HAP in doses of 0.8, 1.2, 1.6, 2.0, 2.4 and 2.8 mg/hr in fifteen male subjects (nine control and six duodenal ulcer), with subcutaneous pentagastrin in doses of

250, 300, 350, 400 and 450 µg in fifteen male subjects (four control and eleven duodenal ulcer) and with intravenous pentagastrin in doses of 50, 100, 150 and 200 µg/hr in twelve male subjects (four control and eight duodenal ulcer).

Gastric aspirate was obtained through 14 or 16 Fr Levine tube by continuous hand suction for 1 hr during subcutaneous tests and for 2 hr during intravenous tests. Details of the procedure are given in a previous study (Desai, Zaveri & Antia, 1970a). Pepsin estimation was performed in each half-hour sample by the method of Hunt (Hunt, 1948) using plasma as substrate; the blue colour with Folin and Ciocalteu reagent was measured on a colorimeter. In our laboratory, 1 mg of crystalline pepsin (Worthington Biochemical, USA) showed 140 Hunt units of peptic activity.

Results

Subcutaneous histamine tests (SHT)

On increasing the doses of HAP from 1.6 to 2.0, 2.0 to 2.4 and 2.4 to 2.8 mg, the mean and standard deviation (SD) of differences of pepsin output on paired 't' testing showed an increase of 1.8 ± 1.8 ($P < 0.01$), 1.46 ± 1.6 ($P < 0.01$) and 1.46 ± 2.56 ($P < 0.05$) kilounits/hr respectively. Further increase in dosage of HAP from 2.8 to 3.2 mg showed a significant decrease of 1.38 ± 2.5 kilounits/hr of pepsin output ($P < 0.05$) (Table 1). The minimal dose of

TABLE 1. Dose-response curves on subcutaneous histamine test in twenty-two subjects for pepsin estimation

	Dose of subcutaneous HAP (mg)				
	1.6	2.0	2.4	2.8	3.2
Mean and SD of differences of pepsin output (Kilounits/hr)	1.8 ±	1.46 ±	1.46 ±	1.38 ±	1.38 ±
<i>P</i>	(18) *	(19)	(18)	(18)	(18)
	<0.01	<0.01	<0.05	<0.05	<0.05

* The figures in brackets refer to paired 't' test in each group (Tables 1-4).

subcutaneous HAP for maximal pepsin secretion was 2.8 mg. A supramaximal dose of 3.2 mg caused a significant reduction of pepsin output.

Intravenous histamine tests (IHT)

On increasing the doses of intravenous HAP from 0.8 to 1.2, 1.2 to 1.6 and 1.6 to 2.0 mg/hr, the mean and SD of differences of pepsin output on paired 't' testing showed an increase of 2.14 ± 2.76 ($P=0.05$), 0.22 ± 1.95 ($P>0.05$) and 0.24 ± 2.27 ($P>0.05$) kilounits/30 min respectively. Further increase in dosage of HAP from 2.0 to 2.4 and 2.4 to 2.8 mg/hr showed a reduction of 0.61 ± 1.93 ($P>0.05$) and 1.23 ± 1.17 ($P<0.01$) kilounits/30 min respectively (Table 2). The minimal dose of intravenous HAP for maximal pepsin secretion was 1.2 mg/hr while a supramaximal dose of 2.8 mg/hr caused a significant reduction of pepsin output.

Subcutaneous pentagastrin tests (SPT)

On increasing the doses of pentagastrin from 250 to 300 and 300 to 350 μg , the mean and SD of differences of pepsin output showed an increase of 2.11 ± 2.77 ($P=0.05$) and 0.11 ± 4.57 ($P>0.05$) kilounits/hr respectively. Further increase in dosage from 350 to 400 and 400 to 450 μg caused a reduction of pepsin output of 0.52 ± 4.28 ($P>0.05$) and 0.58 ± 2.73 ($P>0.05$) kilounits/hr respectively (Table 3). The reduction of pepsin output (1.94 ± 5.15 kilounits/hr) on increasing the dose from 350 to 450 μg

was also not significant ($P>0.05$). The minimal dose of subcutaneous pentagastrin for maximal pepsin secretion was 300 μg .

Intravenous pentagastrin tests (IPT)

On increasing the doses of pentagastrin from 50 to 100 $\mu\text{g/hr}$ and 100 to 150 $\mu\text{g/hr}$, the mean and SD of differences of pepsin output showed a rise of 0.93 ± 1.24 ($P<0.05$) and 0.63 ± 1.36 ($P>0.05$) kilounits/30 min respectively. Further increase of dosage from 150 to 200 $\mu\text{g/hr}$ caused a reduction of 0.35 ± 1.86 ($P>0.05$) kilounits/30 min (Table 4). The minimal dose of intravenous pentagastrin for maximal pepsin secretion was 100 $\mu\text{g/hr}$.

Discussion

Dose-response curves for maximal pepsin secretion have been obtained with subcutaneous pentagastrin in two control subjects (Makhlouf *et al.*, 1966) and with intravenous pentagastrin and histamine in three control subjects (Berstad & Patersen, 1971) but the minimal doses for maximal pepsin secretion were not obvious as only a few subjects were studied. In the present study, the minimal doses for maximal pepsin secretion were 2.8 mg HAP on SHT, 1.2 mg/hr HAP on IHT, 300 μg pentagastrin on SPT and 100 $\mu\text{g/hr}$ pentagastrin on IPT. The results showed that the minimal subcutaneous doses for maximal pepsin secretion were identical with these reported for maximal acid secretion (Desai *et*

TABLE 2. Dose-response curves on intravenous histamine test in fifteen subjects for pepsin estimation

	Dose of intravenous histamine (mg/hr)					
	0.8	1.2	1.6	2.0	2.4	2.8
Mean and SD of differences of pepsin output (Kilounits/30 min)	2.14 \pm 2.76 (8)*	0.22 \pm 1.95 (12)	0.24 \pm 2.27 (8)	-0.61 \pm 1.93 (10)	-1.23 \pm 1.17 (11)	
P	=0.05	>0.05	>0.05	>0.05	<0.01	

* The figures in brackets refer to paired 't' test in each group.

TABLE 3. Dose-response curves with subcutaneous pentagastrin in fourteen subjects for pepsin estimation

	Dose of subcutaneous pentagastrin (μg)				
	250	300	350	400	450
Mean and SD of differences of pepsin output (Kilounits/hr)	2.11 \pm 2.77 (9)	0.11 \pm 4.57 (10)	-0.52 \pm 4.28 (12)	-0.58 \pm 2.73 (9)	
P	=0.05	>0.05	>0.05	>0.05	

* The figures in brackets refer to paired 't' test in each group.

TABLE 4. Dose-response curves with intravenous pentagastrin test in twelve subjects for pepsin estimation

	Dose of intravenous pentagastrin ($\mu\text{g/hr}$)			
	50	100	150	200
Mean and SD of differences of pepsin output (Kilounits/30 min)	0.93 \pm 1.24 (12)*	0.63 \pm 1.36 (11)	-0.35 \pm 1.86 (10)	
P	<0.05	>0.05	>0.05	

* The figures in brackets refer to paired 't' test in each group.

TABLE 5. Comparison of values of maximal pepsin secretion with subcutaneous or intravenous histamine and pentagastrin in two subjects

No.	Route	Histamine acid phosphate (mg)							Pentagastrin (μ g)								
		0.8	1.2	1.6	2.0	2.4	2.8	3.2	50	100	150	200	250	300	350	400	450
1	Subcutaneous	—	—	6.8	7.2	7.6*	6.2	6.1	—	—	—	—	—	—	6.6	8.2	10.8*
	Intravenous	8.8*	8.5	—	7.5	7.5	7.2	—	5.0	5.8	7.2*	5.8	—	—	—	—	—
2	Subcutaneous	—	—	7.5	7.2	7.9	7.0	8.4*	—	—	—	—	8.1	9.7	9.9*	9.1	9.9
	Intravenous	5.8	5.5	7.3	8.9	9.6*	8.4	—	7.3	9.0*	8.6	7.8	—	—	—	—	—

* Highest value, figures in kilounits/30 min.

al., 1969; Desai, Zaveri & Antia, 1972). However, the minimal intravenous doses for maximal pepsin secretion, 1.2 mg/hr HAP and 100 μ g/hr pentagastrin, are smaller than those required for maximal acid secretion, 2.0 mg/hr HAP and 150 μ g/hr pentagastrin (Desai, Zaveri & Antia, 1970b; Desai, Zaveri, Dalvi & Antia, 1972). That minimal doses of intravenous pentagastrin and HAP for maximal pepsin secretions are lower than those for maximal acid secretion was reported by Berstad & Patersen (1971).

Supramaximal doses of subcutaneous and intravenous HAP caused a significant partial inhibition of pepsin secretion (Tables 1 and 2). Higher doses of pentagastrin also caused reduction of pepsin secretion but the differences were not significant (Tables 3 and 4). Pepsin secretion was not reduced with intravenous pentagastrin up to 7 μ g/kg/hr (Berstad & Patersen, 1971) but doses higher than 8 μ g/kg/hr showed a tendency to fall (Makhlouf *et al.*, 1966).

In humans, histamine (Hirschowitz, London & Pollard, 1957), histalog (Wormsley, Mahoney & Ng, 1966) and pentagastrin (Makhlouf *et al.*, 1966) stimulate pepsin secretion and values with any stimulus are comparable. In contrast, maximal values of pepsin secretion were shown to be appreciably lower with pentagastrin than histamine (Berstad & Patersen, 1971). In the present study, the values of maximal pepsin secretion in two subjects with HAP or pentagastrin by either route were comparable (Table 5).

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