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Aminopyrine · 抗히스타민 劑混合物의 吸收에 關한 硏究

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S. H. Han, M. H. Lee, S. H. Min, S. K. Kim, C. H. Woo; Studies on the Absorption of Mixed Compounds of Aminopyrine Antihistamic Agent.

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The absorption of Aminopyrine from the small intestine of a rat in combination with antihistamic agent, Diphenhydramine, Pheniramine, Tripelennamine and Diphenhydramine respectively, was examined.

Through the rat small intestine canal, a definite quantity of a sample solution comprising 0.5 mM of Aminopyrine and 0.1 mM of each antihistamic agent in phosphate buffer solution (pH=7.4) was perfused through the rat small intestine at rate 5ml per minute.

The samples of the circulating solution were taken out after 5 minutes of the perfusion to give initial concentration and every 30 minutes for 3 hours. The amount of residual Aminopyrine in the solution was determined photometrically at 720 mμ by using 0.4% potassium ferricyanate solution and 1% ferric nitrate in 0.1N nitric solution.

The mixed compounds of Aminopyrine with antihistamic agent, such as Aminopyrine with Diphenhydramine, Aminopyrine with Pheniramine, Aminopyrine with Tripelennamine and Aminopyrine with Chlorpheniramine showed more increased absorption than Aminopyrine alone.

The absorption rate constants and apparent permeability coefficients of the mixed compounds were shown in detail.

結　　論

醫藥品의 吸收에 關한 硏究는 Brodie[1], Schanker[2], Hogben[3], Rall[4], Kakemi[5,6] 및 Nogami[7-9] 등에 依하여 硏硏되었고 Aminopyrine의 吸收 및 排泄에 對해서는 Naito[10]가 報告한 바 있으며 또한 Aminopyrine 分子化合物의 吸收에 關한 硏究는 韓[11]이 報告하고 있다.

一般的으로 醫藥品의 併用에 關한 硏究는 Bürgi[12]가 單一藥物에서 期待되는 藥效가 2種 以上 併用投與되었을 때 그 主藥의 藥理作用 및 毒性을 增強 또는 減少시킨다는 事實을 提唱한 以來, 藥物併用에 依한 藥理作用의 機構에 對해서 生體細胞의 感受性, 蛋白結合, 複合

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體生成과 藥物代謝 等의 面에서 檢討되고 있으나, 아직 不明한 點이 많아 今後의 研究가 必要로되고 있는바 著者들은 醫藥品併用藥의 生體에 對한 여러가지 影響을 檢討하여 더욱 有用한 併用藥의 開發을 目的으로 Aminopyrine과 併用藥物로서 흔히 處方中에서 散見되는 抗히스타민劑中 Aminoether系·Ethylenediamine系 및 Monoamine系의 藥物을 取하여 吸收實驗을 하여 Pharmacokinetics面에서 檢討한바 知見을 얻었기에 報告하는 바이다.

實 驗

1. 試 料

Aminopyrine(E. Merck) Diphenhydramine HCl(K.P.) Tripelennamine. HCl(K.P.) Pheniramine maleate(Schering Co.) Chlorpheniramine maleate(K.P.)

2. 還流溶液의 調製

Aminopyrine 0.5mM에 該當하는 量과 Antihistamic Agent 各各 0.1mM에 該當하는 量을 取하여 phosphate Buffer pH(7.4)에 녹여 調製하였다.

3. Rat 小腸管에서의 in situ 에 依한 還流試驗

Shanker 등의 方法에 따른 金[13]의 方法에 準하여 in situ Loop's Circulation 試驗을 行하였다.

4. Aminopyrine의 定量

還流試驗에서 一定時間마다 採取한 還流液 0.5ml로 Naito[10]의 方法에 따라 Aminopyrine을 定量하였다.

實驗結果 및 考察

還流法에 依한 Rat 小腸에서의 Aminopyrine과 Mixed compound of Aminopyrine Diphenhydramine, Aminopyrine Tripelennamine, Aminopyrine Pheniramine, Aminopyrine Chlorpheniramine의 吸收를 吸收速度式에 따라서 算出했다.

即 腸內에서의 藥物透過量 q, 腸管의 表面積 A, 透過係數 p, 藥物의 濃度 C로 할 때 Ficks의 法則에 따라서 Passive diffusion을 한다면 藥物의 血中濃度가 濃度 c에 比하여 充分히 작을 때는 透過速度는 濃度 c에 比例함으로

$$q = Apc \quad \cdots\cdots(1)$$

腸內에서의 吸收 q는 還流中의 藥液의 總容積 V, 그 濃度를 c로 한다면 다음과 같은 式으로 된다.

$$q = -V\frac{dc}{dt} \quad \cdots\cdots(2)$$

(1)+(2)에서

$$-V\frac{dc}{dt} = Apc \quad \cdots\cdots(3)$$

$$-\frac{dc}{dt}=\frac{Apc}{V} \quad \cdots\cdots(4)$$

$-\frac{dc}{dt}$는 直接測定이 不能함으로 이를 積分하기 위하여 變形하면

$$\frac{dc}{c}=-\frac{Apdt}{V} \quad \cdots\cdots(5)$$

兩邊을 積分하면

$$\int\frac{dc}{c}=-\frac{Ap}{V}dt \quad \cdots\cdots(6)$$

$$l_n\frac{c}{c_0}=-\frac{Apt}{V} \quad \cdots\cdots(7)$$

이것을 常用對數로 고치면

$$\log\frac{c}{c_0}=-0.434\times\frac{Ap}{V}\cdot t=-0.434kt \cdots\cdots(8)$$

로 된다.

또한 腸管의 有效表面積 A는 腸管의 길이 l, 容積을 v로 한다면

$$A=2\sqrt{\pi l v}\ ^{(8)} \quad \cdots\cdots(9)$$

이며 이로부터 (8)式을 使用하여 p를 算出할 수 있다.

이 實驗에서 Aminopyrine 및 Mixed Compounds of Aminopyrine Antihistamic agent의 吸收率은 Table I~V 및 Fig. 1~5와 같으며 一次反應速度式에 準하여 吸收됨을 알 수 있다.

Teble I. Absorption Rate of Aminopyrine(in situ)

Time(min.)	Remaining drug	Absorption Rate	$\log\left(\frac{c}{c_0}\right)$	k	p(cm/min.)	κ(min.$^{-1}$)
30	89.1	10.9	−0.0501	1.67×10^{-3}	3.23×10^{-3}	3.85×10^{-3}
60	80.4	19.6	−0.0947	1.57	3.16	4.20
90	71.0	29.0	−0.1487	1.65	3.30	3.81
120	64.6	35.4	−0.1898	1.58	3.11	3.64
150	58.5	41.5	−0.2328	1.55	3.22	3.57
180	52.3	47.7	−0.2815	1.56	3.20	3.60
mean				1.59×10^{-3}	3.26×10^{-3}	3.77×10^{-3}

k; slop. p; Permeability coefficient. κ; velocity constant.
Results are given as mean value from six experiments.

Table II. Absorption Rate of Mixed compound of Aminopyrine Diphenhydramine(in situ)

Time(min.)	Remaining drug	Absorption Rate	$\log(c/c_0)$	k	p(cm/min.)	κ(min.$^{-1}$)
30	88.3	11.7	0.0540	1.80×10^{-3}	3.42×10^{-3}	4.15×10^{-3}
60	77.0	23.0	0.1135	1.89	3.45	4.35
90	68.5	31.5	0.1643	1.82	3.44	4.21
120	60.6	39.4	0.2175	1.81	3.32	4.17
150	54.0	46.0	0.2676	1.78	3.12	4.10
180	48.3	51.7	0.3161	1.75	3.30	4.04
mean				1.80×10^{-3}	3.39×10^{-3}	4.17×10^{-3}

Table III. Absorption Rate of Mixed Compound of Aminopyrine Pheniramine(in situ)

Time(min.)	Remaining drug	Absorption Rate	$\log(c/c_0)$	k	p(cm/min.)	κ(min.$^{-1}$)
30	86.0	14.0	0.0655	2.18×10^{-3}	4.25×10^{-3}	5.03×10^{-3}
60	74.3	25.7	0.1290	2.15	4.20	4.95
90	64.5	35.5	0.1904	2.11	4.05	4.87
120	56.6	43.4	0.2472	2.06	4.04	4.74
150	49.0	51.0	0.3098	2.07	4.02	4.75
180	43.5	56.5	0.3615	2.00	4.01	4.62
mean				2.09×10^{-3}	4.08×10^{-3}	4.76×10^{-3}

Table IV. Absorption Rate of Mixed Compound of Aminopyrine Tripelennamine(in situ)

Time(min.)	Remaining drug	Absorption Rate	$\log(c/c_0)$	κ	p(cm/min.)	κ(min.$^{-1}$)
30	84.3	15.7	0.0742	2.47×10^{-3}	4.72×10^{-3}	5.69×10^{-3}
60	72.5	27.5	0.1397	2.32	4.50	5.36
90	60.2	39.8	0.2204	2.44	4.52	5.64
120	52.0	48.0	0.2840	2.36	4.65	5.45
150	44.5	55.5	0.3516	2.34	4.80	5.40
180	38.3	61.7	0.4168	2.31	4.65	5.33
mane				2.37×10^{-3}	4.63×10^{-3}	5.47×10^{-3}

Table V. Absorption Rate of Mixed Compound of Aminopyrine Chlorpheniramine(in situ)

Time(min.)	Remaining drug	Absorption Rate	$\log(c/c_0)$	k	p(cm/min.)	κ(min.$^{-1}$)
30	83.0	17.0	0.0809	2.69×10^{-3}	5.17×10^{-3}	6.21×10^{-3}
60	69.1	30.9	0.1605	2.67	5.25	6.16
90	58.3	41.7	0.2343	2.60	5.31	6.00
120	49.5	50.5	0.3054	2.54	5.34	5.96
150	41.8	58.2	0.3788	2.52	5.15	5.81
180	35.0	65.0	0.4559	2.53	5.08	5.83
mean				2.59×10^{-3}	5.22×10^{-3}	5.99×10^{-3}

k; slope k; permeability coefficient κ; velocity constant

Results are given as mean value from six experiments.

以上의 結果로 보아 Aminopyrine自體보다 Mixed compounds of Aminopyrine Antihistamic agent의 Rat小腸에서의 吸收率은 pH 7.4 phosphate Buffer에서는 一般的으로 促進的으로 作用하고 있으며 Aminopyrine에 比하여 Mixed compound of Aminopyrine Diphenhydramine은 1.7%, Aminopyrine pheniramine은 6.5%, Aminopyrine Tripelennamine은 11.7%, Aminopyrine Chlorpheniramine은 15%의 吸收率에 있어서의 上昇을 還流 180分만에 보이고 있으며, 이와 같은 吸收率의 促進은 抗히스타민劑의 鹽酸鹽 또는 有機酸鹽이 pH 7.4의 phosphate

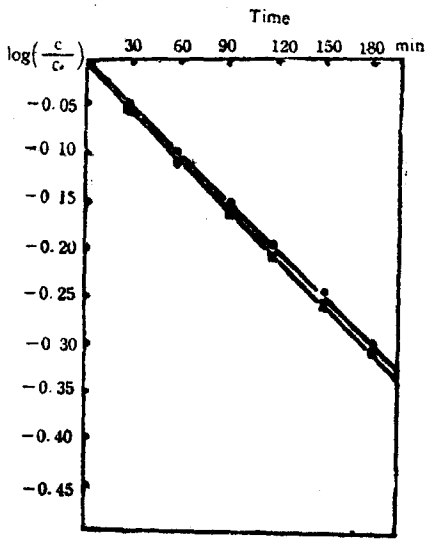

Fig 1. Curve illustrating the linear relationship between the logarithmic function and time in Aminopyrine(.), mixed and in compound of Aminopyrine diphenhydramine (×).

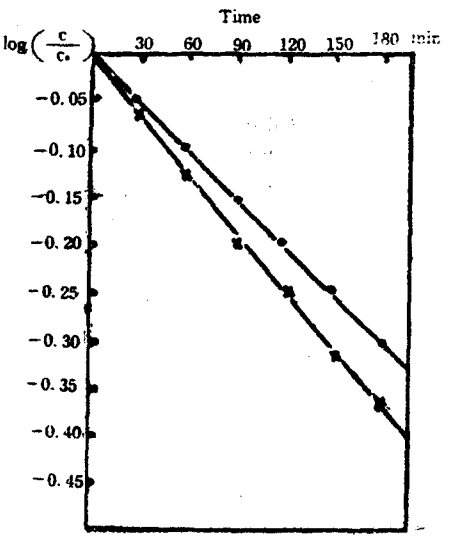

Fig 2. Curve illustrating the linear relationship between the logarithmic function and time in Aminopyrine(.), and in mixed compound of Aminopyrine pheniramine (×).

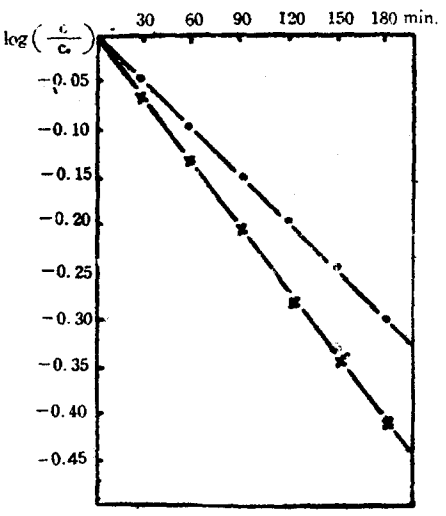

Fig 3. Curve illustrating the linear relationship between the logarithmic function and time in Aminopyrine (.), and in mixed compound of Aminopyrine tripelennamine (×).

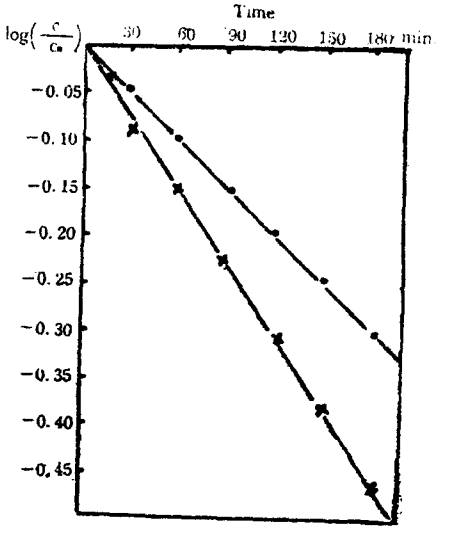

Fig 4. Curve illstrating the linear relationship between the logarithmic function and time in Aminopyrine (.), and in mixed compound of Aminopyrine chlorpheniramine (×)

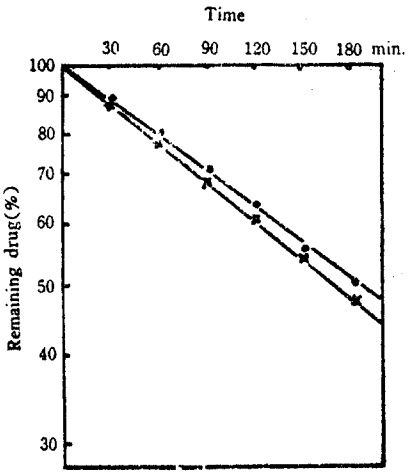

Fig 5. Linear relationship between remaining Aminopyrine(.), and mixture of Aminopyrine-Diphenhydramine(×), in perfusion

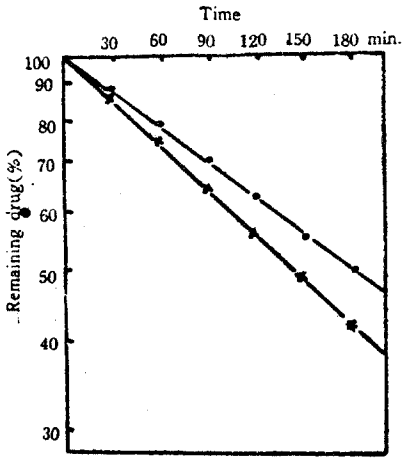

Fig 6. Linear relationship between remaining Aminopyrine(.), and mixture of Aminopyrine-Phenilramine (×), in Perfusion

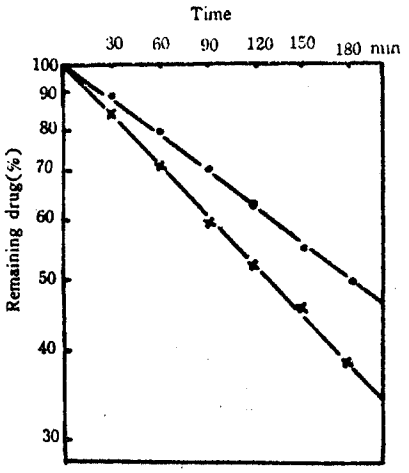

Fig 7. Linear relationship between remaining Aminopyrine(.), and mixture of Aminopyrine-Tripelennamine(×), in perfusion

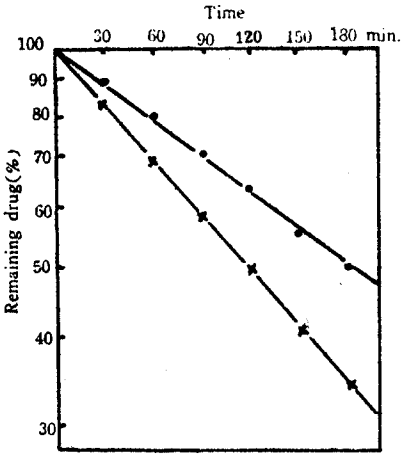

Fig 8. Linear relationship between remaining Aminopyrine(.), and mixture of Aminopyrine-Chlorpheniramine(×), in perfusion

Buffer 溶液中에서는 遊離狀態로 되여 그 脂溶性의 增加가 Aminopyrine과 包合하여 吸收를 增加하는 것으로 思料된다.

또 吸收速度定數는 Mixed compound of Aminopyrine Diphenhydramine 4.17×10^{-3}, Aminopyrine Pheniramine 4.76×10^{-3}, Aminopyrine Tripelennamine 5.47×10^{-3}, Aminopyrine Chlorpheniramine $5.99\times10^{-3}min^{-1}$ 이다.

"Fig. 1~5"의 Slope로부터 求한 Half life는 Aminopyrine이 186分인데 比하여 漸次的으로 短縮되어 Mixed compound of Aminopyrine Diphenhydramine 168分, Aminopyrine pheniramine 144分, Aminopyrine Tripelennamine 127分이고, Aminopyrine Chlorpheniramine은 116分이다.

이로부터 Aminopyrine에다 抗히스타민劑가 處方中에서 配合되어 질때에는 一般的으로 Aminoether系인 Diphenhydramine·HCl에서는 吸收促進作用이 別로 顯著하지 않으나 Ethylenediamine系인 Trilennamine·HCl를 經由하여 Monoamine系인 Pheniramine maleate와 가장 吸收促進作用을 示顯하고 있는 같은 Monoamine系인 Chlorpheniramine maleate임을 알 수 있다.

結 論

1. Circulation method(in situ)에 依한 Rat 小腸에서의 Mixed compounds of Aminopyrine Antihistamic agent의 吸收는 一般的으로 促進的으로 作用하며 Aminoether系보다 Monoamine系인 抗히스타민劑가 Aminopyrine의 吸收를 促進한다.
2. Mixed Compounds of Aminopyrine Antihistamic agent의 吸收速度定數는
   - Aminopyrine Diphenhydramine $4.17\times10^{-3}min.^{-1}$
   - Aminopyrine Pheniramine 4.76×10^{-3} 〃
   - Aminopyrie Tripelennamine 5.47×10^{-3} 〃
   - Aminopyrine Chlorpheniramine 5.99×10^{-3} 〃

   이다.
3. Mixed Compounds of Aminopyrine Antihistamic agent의 透過係數는
   - Aminopyrine Diphenhydramine 3.39×10^{-3}(cm/min.)
   - Aminopyrine Pheniramine 4.08×10^{-3} 〃
   - Aminopyrine Tripelennamine 4.63×10^{-3} 〃
   - Aminopyrine Chlorpheniramine 5.22×10^{-3} 〃

   이다.

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