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PHARMACODYNAMIC AND PHARMACOKINETIC PROFILE OF IMIDAZOLE 2-HYDROXYBENZOATE, A NOVEL ANTIINFLAMMATORY AGENT

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The anti-inflammatory process is a complicated plot of events, in which different cellular and chemical mechanisms, as well as different mediators, are involved. Each mediator has its own range of activity and can interact with the others in a complex way. The overall effect of two different mediators on a specific component of the inflammatory process can be more powerful than the sum of the individual effects (synergism).

Non-steroidal anti-inflammatory drugs (NSAIDs) are pharmacotherapeutic acting substances whose antiphlogistic, analgesic and antipyretic effects are considered to be due to the specific inhibition of the synthesis of some of the above-mentioned mediators through the block of the arachidonic acid cascade. Recently, the substances of this group were carefully supervised in some countries because of their frequent and severe side-effects : some of these have been banned from the market or partially limited as for time of administration and indications.

Imidazole 2-hydroxybenzoate is a novel compound provided with anti-inflammatory activity, proposed as an antiphlogistic, analgesic and anti-pyretic drug in human therapy. The chemical structure is shown in Fig. 1. It is composed of 33.026% imidazole and 66.974% salicylic acid. The imidazole nucleus is often found in biological substrates, mainly in peptide-, protein-, enzyme-, nucleic acid-structures and others; this nucleus has been defined as "servo-pharmacologic agent". It is also interesting to observe that if imidazole and salicylic acid

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are given separately as individual substances they act differently from an equivalent dose of imidazole 2-hydroxybenzoate.

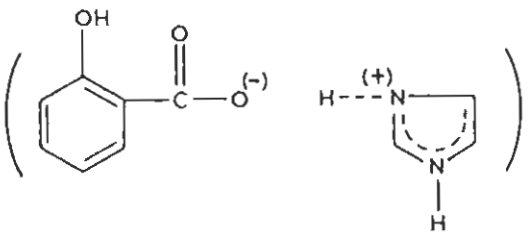

Figure 1. Chemical structure of imidazole 2-hydroxybenzoate

In spite of the availability of numerous really powerful anti-inflammatory agents, new compounds are still needed, especially to meet the various clinical necessities of a long-term treatment in patients suffering from chronic phlogistic diseases. In fact, it must be kept in mind that, particularly in long-term treatments, the choice of the drug does not depend only upon the ability to obtaining therapeutically useful effects but also upon the lack of significant untoward side-effects, which generally go together with a strong inhibition of the prostaglandin pathway. Regarding this aspect, some interesting data from the pharmacology of imidazole 2-hydroxybenzoate deserve particular attention. It must be recalled that modern anti-inflammatory drugs seem to have as their main target the key enzymes of the arachidonic acid cascade : i.e., phospholipase A_2 inhibition, and as a consequence the endoperoxide, hydroperoxide and leukotriene production is obviously limited. On the other hand, for NSAIDs such an activity on phospholipase has not been stated, nor do they seem to be effective on the lipoxygenase pathway : their mechanism of action can be taken back to an inhibitory effect on cyclooxygenase, which is the enzyme converting arachidonic acid to prostaglandins.

It is well to remember that, from the same metabolic pathway substances with pro- and anti-inflammatory activities arise and that the activity of these compounds is characterised by a large-spectrum, conditioning the homoeostatic regulation of various organs and systems.

It is then easily comprehensible how cyclooxygenase inhibition, exerted by the better known NSAIDs and indiscriminately blocking or reducing all kinds of prostaglandins, could be responsible for numerous untoward side-effects (gastric, renal and cutaneous). The need has thus arisen for drugs able to interfere selectively with the arachidonic acid metabolism or, better still, only with the synthesis of those substances deeply involved in the genesis and self-maintenance of a phlogistic status. In fact, this would assure, besides therapeutic efficacy, a better systemic tolerance and possibly, the lack of serious toxic effects in the long-term treatment.

Experimentally, imidazole 2-hydroxybenzoate seems to have these characteristics : a series of pharmacological studies shows that this compound selectively inhibits thromboxane A_2- synthetase so blocking the production of this crucial pro-inflammatory agent. This selective inhibition makes a greater number of endoperoxides available for synthesis of the antiphlogistic PGI_2 and PGE_2. Other experiments indicate that imidazole 2-hydroxybenzoate can form copper-complexes which can exert a scavenging effect on free oxy-radicals. It is also able to affect neutrophil activity : in fact, the drug dose-dependently inhibits, "in vitro", chemotaxis, lysosomal enzyme release and superoxide anions O_2 production by neutrophils isolated from healthy volunteers challenged with a chemotactic peptide.

An overall evaluation of the above data allows to support the conclusion that imidazole 2-hydroxybenzoate exerts its pharmacological effects by different mechanisms which may well cooperate in determining its therapeutic activity. Imidazole 2-hydroybenzoate, for this reason, may play an important role in clinics, since in its indication area (i.e., inflammatory diseases of different genesis) the duration of administration may not be limited so that clinical-biological tolerance has to be considered of great importance.

As expected, due to the ionic bond between the components of this organic salt, it was not possible to find imidazole 2-hydroxybenzo-

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ate, as such, in plasma and urine. For this reason, a pilot study with the aim to set up new methods to detect imidazole, salicylic acid and their metabolites was carried out. Subsequently, a further more extensive trial was performed : 36 healthy male volunteers received imidazole 2-hydroxybenzoate, tablets and drops, according to a cross-over design, in order to assess the pharmacokinetic profile of the drug both after single and multiple dosing. For single dosing study, the volunteers received either one 750 mg tablet or 40 drops (equivalent to 800 mg of active substance). For the multiple dosing study they received the same dose on day 1, and then, after a wash-out period of 48 hrs, dosing was repeated thrice daily (every 8 hrs) for three days ; on the 4th day, only one dose, the 1st one, was administered.

The imidazole metabolites (hydantoin and hydantoin acid) as well as gentisinic acid (salicylic acid metabolite) were present in plasma and urine according to chromatographic assays but all under the limit of detection (0.5 µg/ml) anyway they did not interfere with the other assays.

In Tables 1-3 the main plasma pharmacokinetic parameters of imidazole, salicylic acid and salicyluric acid (the most important metabolite of salicylic acid) are summarized for both pharmaceutical forms and for single and multiple dosing.

The protein binding of salicylic acid is about 80-85% and that of imidazole 5-15%. The relative bioavailability (tablets vs.drops) was as follows :

	single dosing	multiple dosing (last dose)
Imidazole	138 %	113 %
Salicylic acid	148 %	128 %

From the above results it can be stated that :

1. Imidazole does not interfere with the pharmacokinetics of salicylic acid, whose concentrations appeared to be comparable to those reported in the literature and in

the range of the therapeutic ones.

2. Both components of the molecule did not show any accumulation tendency, even when administered in multiple dosing.

3. Tablets gave higher AUCs, and therefore they seem better absorbed than drops.

CONCLUSION

The pharmaco-toxicological profile of imidazole 2-hydroxybenzoate is clearly defined and, as far as the mechanism of action is concerned, offers a newer and safer pharmacological approach to the treatment of inflammation when compared with traditional NSAIDs. In fact, the selective blockade of TXA_2 production, together with the lack of any effect on cyclooxygenase i.e., on the prostaglandin synthesis, allows to affect the complex play of phlogosis without interfering with the functions of organs, classic victims of irreversible and strong prostaglandin inhibition (kidney and stomach), especially in particular type of patients.

On the basis of this pharmacological premises, a consistent amount of clinical trials have been carried out in different clinical conditions, characterized by the presence of acute or chronic inflammations, in children, in adults as well as in elderly patients. So far 629 patients have been treated in clinical studies, for periods ranging from 1 to 168 days (24 weeks). The trials were conducted according to well designed protocols in open or blind conditions. Adequate parameters were choosen according to the different kinds of the studied inflammatory diseases. Overall, the drug resulted satisfactorily effective, also when compared to well-known and active traditional NSAIDs, as ASA, piroxicam, ibuprofen, sulindac and others.

On the whole population treated with imidazole 2-hydroxybenzoate (629 patients) the percentage of side-effects was 6.84%. This per-

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centage incidence is clearly lower than that of the most used ones. It should be especially mentioned that the good tolerability of imidazole 2-hydroxybenzoate has been documented also in patients commonly considered at risk, as diabetics with incipient nephropathy, hypertensives, and elderly. The low incidence of side-effects recorded in the 6 months study is relevant for the perspectives of long-term treatments, where the compliance of the patients may be considered as, if not even more, important as the drug efficacy, in view of a successful control of the disease.

For all these reasons, imidazole 2-hydroxybenzoate is indicated for the treatment of acute, subacute and chronic inflammations, also in patients usually considered at risk (diabetics, hypertensives, children, and elderly patients). The recommended posology is 1-2 x 20 mg/kg/day in children, and 2-3 x 750-800 mg/day in adults.

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Table 1. Summary of the essential pharmacokinetic parameters (plasma mean values and SD) of imidazole in imidazole 2-hydroxybenzoate tablets and drops.

Imidazole		C_{max}	T_{max}	AUC_0^∞	$t_{½\beta}$
Single dose-tablets		3.59 ± 0.96	0.79 ± 0.54	16.00 ± 7.10	2.98 ± 1.13
Multiple dose-tablets	F	2.87 ± 0.84	1.04 ± 0.50	14.53 ± 4.02	2.85 ± 1.25
	L	3.11 ± 0.78	0.68 ± 0.51	8.93 ± 3.15	1.86 ± 0.78
Single dose-drops		3.30 ± 1.22	0.71 ± 0.59	12.29 ± 9.96	2.48 ± 1.19
Multiple dose-drops	F	2.67 ± 1.22	0.96 ± 0.67	13.29 ± 4.12	3.47 ± 2.64
	L	2.30 ± 0.61	0.51 ± 0.52	7.40 ± 3.47	2.12 ± 2.91

F = first dose ; L = 10th dose (last dose). From (1).

The peak plasma concentrations of imidazole (ranging 3.30-3.59 µg/ml for single dose and 2.30-3.11µg/ml for the last multiple dose) were reached fast (T_{max} ranging 0.71-0.79 hrs for single dose and 0.51-1.04 hrs for the last multiple dose) and levels decreased rapidly ($t_{½\beta}$ ranging 2.48-2.98 hrs for single dose and 1.86-3.47 hrs for the last multiple dose) ; these data were similar for both galenic formulations and give no evidence for any accumulation tendency. The renal elimination of imidazole was about 10-15%.

Table 2. Summary of the essential pharmacokinetic parameters (plasma mean values and SD) of salicylic acid in imidazole 2-hydroxybenzoate tablets and drops.

Salicylic acid		C_{max}	T_{max}	AUC_0^∞	$t_{1/2\beta}$
Single dose-tablets		38.50 ± 16.38	0.90 ± 0.87	262.31 ± 118.25	6.46 ± 3.79
Multiple dose-tablets	F	41.56 ± 12.16	0.93 ± 0.78	302.33 ± 108.34	6.28 ± 2.94
	L	52.23 ± 21.44	1.47 ± 1.41	464.00 ± 286.02	6.40 ± 3.26
Single dose-drops		30.31 ± 8.03	1.16 ± 0.75	188.63 ± 62.58	4.63 ± 2.35
Multiple dose-drops	F	43.86 ± 18.51	0.96 ± 1.03	277.52 ± 166.91	6.76 ± 6.15
	L	58.39 ± 23.17	1.36 ± 0.80	386.61 ± 194.34	5.60 ± 3.66

The peak plasma concentrations of salicyclic acid were (30.31-38.50 µg/ml for single dose and 41.56-58.39 µg/ml for the last multiple dose) in the range of therapeutic effective ones; the peaks were reached (T_{max} 0.90-1.16 hrs for the single dose and 0.93-1.47 hrs for the last multiple dose) almost as fast as for imidazole and they decreased slightly slower ($t_{1/2\beta}$ values ranging 4.63-6.46 hrs for the single dose and 5.60-6.76 hrs for the last multiple dose). These results, almost identical for both galenic formulations, show again no evidence of accumulation tendency and are in good agreement with published data. From (1).

Table 3. Summary of the essential pharmacokinetic parameters (plasma mean values and SD) of salicyluric acid in imidazole 2-hydroxybenzoate tablets and drops.

Salicyluric acid		C_{max}	T_{max}	AUC_0^∞	$t_{1/2\beta}$
Single dose-tablets		2.75 ± 0.81	0.96 ± 0.65	53.18 ± 36.68	12.39 ± 8.56
Multiple dose-tablets	F	1.35 ± 0.33	0.94 ± 0.88	30.47 ± 11.51	12.77 ± 4.55
	L	2.06 ± 0.91	1.37 ± 1.21	40.94 ± 16.78	11.26 ± 5.90
Single dose-drops		2.15 ± 0.60	1.10 ± 0.99	64.61 ± 31.80	20.79 ±12.34
Multiple dose-drops	F	1.69 ± 0.87	1.21 ± 1.36	24.55 ± 17.71	9.28 ± 8.99
	L	2.10 ± 0.89	1.27 ± 1.15	40.71 ± 28.58	13.16 ±11.60

As for salicyluric acid, C_{max} and T_{max} were similar to those of imidazole and salicylic acid, while $t_{1/2\beta}$ was longer, as expected since the biotransformation of salicylic acid in salicyluric acid is relevant and also very rapid. From (1).