the
PHARMACEUTICAL JOURNAL
A Royal Pharmaceutical Society publication

| News | Pharmaceutical Journal

PJ pharmaceutical-journal.com/20004115.article

The Pharmaceutical Journal 10 MAR 2001

The Pharmaceutical Journal Vol 266 No 7138 p322-323
March 10, 2001

Articles

Changing the salt, changing the drug

By Glynis Davies, BSc, MRPharmS

Changing the salt form of a drug affects its clinical efficacy and safety. This article discusses the potential issues related to the use of different salts of drugs

Changing a drug from its free base or acid to a salt form is commonly done to improve its kinetics, absorption or physicochemical properties (eg, stability, hygroscopicity and flowability). Changing the salt form of a drug is a recognised means of modifying its chemical and biological properties without modifying its structure. Different salts of the same active drug are distinct products with their own chemical and biological profiles that underlie differences in their clinical efficacy and safety.

There is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct. The literature contains many examples of salt forms that differ in the rate of absorption, toxicity and stability of the active drug.

Salt formation

Salts are formed by the reaction of an acid with a base. Any compound with the characteristics of either an acid or a base can, in theory, form a salt, but whether or not a salt is formed depends on the relative strength of the acid or base. When a drug is formulated as a salt, the particular salt form determines the physiochemical properties of the product: stability, solubility and dissolution rate. These properties influence how the drug is handled by the body: how it is absorbed, distributed, eliminated and excreted. The biological activity of a drug at its target site depends not only on its structure and effect at that site, but also on how readily it can reach the site and how readily it is removed from it.

Selecting an appropriate salt form for a drug is an important factor in the early stages of new drug development.[1] The monoprotic hydrochlorides are the most frequent choice of anionic salt-forming radicals, with hydrochloride salts outnumbering sulphates by nearly six to one and forming the largest percentage of salts in use.[2] A decision to change the salt form at a later stage introduces the need to repeat toxicological, formulation and stability tests, with obvious implications for the overall development and production time for the new pharmaceutical product.

Once a drug has been marketed, there may be sound reasons for reformulating it in a different salt form to change its physicochemical properties. An example is provided by the analgesic propoxyphene, which was originally formulated as a hydrochloride salt. Propoxyphene was widely used in a fixed-dose combination with aspirin, but since aspirin proved to be unstable in close physical contact with propoxyphene hydrochloride, an additional step in the manufacturing process was needed to separate the two analgesics. When propoxyphene was reformulated as a napsylate salt, there was no problem of aspirin instability. The relative insolubility of the napsylate salt form compared with the hydrochloride was also an advantage, as it reduced the potential for parenteral abuse of propoxyphene.

Substitution of one salt form of a drug for another can also change the rate of absorption and other pharmacokinetic variables, as well as toxic potential and stability, and all these properties can affect the biological activity of a drug and the clinical use of the formulation.

Rate of absorption

Salts differ in their solubility profiles and dissolution rates, which affect the rate of absorption of the drug and, in turn, the onset, duration, and intensity of its effect.[2] The bioavailability of a drug can therefore be modified by administering it in a different salt form. For example, a study of the relative bioavailability of the vasodilator naftidrofuryl in oxalate and citrate salt forms has shown that the relative rate of absorption is higher for the citrate than for the clinically used oxalate form of the drug.[3]

An example of salt substitution changing the intensity of biological response to a drug is again provided by propoxyphene. This established analgesic was first marketed in the United States in the form of a hydrochloride salt more than 40 years ago. When it was reformulated, the new napsylate salt form was found to have greater potency and a longer duration of action than the hydrochloride, attributable to differences in the rates of absorption of the two salt forms.[4,5] Another example of the variation in biological activity with salt form is provided by calcium preparations. Brand-name preparations, each containing a different calcium salt with a different absorption rate, are reported to vary significantly in their ability to suppress secretion of parathyroid hormone.[6] This has implications for their clinical use as calcium supplementation in osteoporosis.

Moving from clinical practice to veterinary medicine, a further example is provided by the anthelmintic pyrantel. The pamoate salt of pyrantel is reported to be three times as effective as the citrate against large bowel parasites, including resistant strains, because of its lower rate of absorption and consequently greater retention in the gastrointestinal tract.[7]

Toxicity

Some cations and anions are known to be associated with toxic effects and will contribute to the intrinsic toxicity of the salt form. For example, lithium cations have no toxic effect in small quantities but when ingested in large amounts can cause irreversible damage to the kidney. Similarly, tartrate anions, which are usually absorbed only minimally from the gastrointestinal tract, can cause renal damage if they reach the circulation in high concentrations.[2] In addition, pravadoline maleate caused renal tubular lesions in the dog, as a result of maleic acid formed from the maleate anion.[8]

Changing the salt form of a drug can reduce its toxic potential. Typically, a salt that is slowly absorbed in the gastrointestinal tract is less toxic than one with a more rapid rate of absorption. For example, propoxyphene napsylate has an acute oral toxicity half that of propoxyphene hydrochloride when given to rats or mice in equimolar doses; this is due to the more gradual absorption of the napsylate.[9] Furthermore, in animal models, the napsylate appears to lack the convulsant properties of the hydrochloride.

Local irritancy Different salt forms can differ in their capacity to cause oesophageal irritation. For example, alprenolol in the form of the hydrochloride salt has an irritant effect on the oesophagus and can cause oesophageal ulceration in humans, whereas alprenolol benzoate has no irritant effects.[10] The difference in

ulcerogenic potential has been related to the difference in solubility of the salts: alprenolol hydrochloride is highly water soluble and therefore may cause local damage due to local absorption, whereas alprenolol benzoate has low water solubility.

Different salt forms can also differ in the level of irritancy to the gastrointestinal tract, which may result in ulceration or bleeding. Nitrate anions are known to cause local irritancy to the gastrointestinal tract leading to nausea and gastric distress.[2] Lithium salts irritate the gastrointestinal mucosa, an effect due predominantly to the anion moiety rather than the lithium cation. The effect is more marked, with greater discomfort to the patient, the greater the amount of anion administered.[11]

Reaction products Different salt forms of a drug can differ in toxicity because of reaction products in their manufacture. Reaction between the cation or anion moiety of the salt and impurities associated either with the active drug or arising from the manufacturing process can result in the formation of toxic products. For example, formic acid has relatively low intrinsic toxicity, but its salts are often contaminated with highly toxic methyl and ethyl formate esters, which are reaction-solvent side products.[12]

Stability

The particular salt form of a drug can affect its stability. For example, the stability of a drug formulated for administration as tablets can be affected by the hygroscopicity of the salt form. Salts of mineral acids such as hydrochlorides, sulphates and methane sulphonates are highly polar. The polar ionised groups exposed on crystal surfaces create a highly hydrophilic surface favouring wettability and leading to hygroscopicity.[13] In turn, this can reduce stability, particularly if the drug is susceptible to hydrolytic degradation.

Stability is also influenced by the hydrophobicity of the salt-forming acid. The formation of salts with low water solubility is a means of increasing the chemical stability of a drug that is sensitive to heat and moisture, such as xilobam. Stability is an issue for xilobam tablets containing the highly soluble sulphate salt of the drug, because the salt is readily hydrolysed and dissolves in surface moisture. However, when the salt-forming acid is aryl sulphonic acid, the hydophobic aryl group presents a barrier to dissolution and this salt form of xilobam is more stable when exposed to high temperature and humidity.[14]

Thermal stability can vary from one salt form of a drug to another. For example, the hydrochloride salt of lincomycin undergoes thermal degradation whereas the cyclamate is significantly more stable.[15] Similarly, the procaine salt of penicillin G has good aqueous stability but poor thermal stability, unlike sodium or potassium salts of the antibiotic, which can withstand prolonged exposure (four days) to temperatures of 100C.[16]

Conclusion

Different salt forms of a drug differ in ways that can impact on their clinical efficacy and safety. Changing the salt form varies the solubility and rate of dissolution of a drug, which in turn affects its bioavailability, pharmacokinetic profile, toxicity, and chemical stability. Early selection of an appropriate salt form in the development of a new drug will influence the timely completion of drug development and production, an important factor in accelerating the process of drug discovery.

Substitution of one salt form for another can accelerate the onset and duration of biological activity of a drug and is a recognised means of reducing its toxic potential or improving its chemical stability. It is important to remember, however, that since changing the salt can dramatically change the properties of a drug, every salt form of a drug should be considered as a new medicinal product and tested appropriately before it is released for use in clinical practice.

References

1.	Tong W-Q, Whitesell G. In situ salt screening: a useful technique for discovery support and preformulation studies. Pharm Dev Technol 1998;3:215-23.
2.	Berge SM, Bighley LD, Monkhouse DC. Pharmaceutical salts. J Pharm Sci 1977;66:1-19.

3.	Walmsley LM, Taylor T, Wilkinson PA, Brodie RR, Chasseaud LF, Alun-Jones V et al. Plasma concentrations and relative bioavailability of naftidrofuryl from different salt forms. Biopharm Drug Dispos 1986;7:327-34.
4.	Baptisti A, Gruber CM, Santos EL. The effectiveness and side effect liability of propoxyphene hydrochloride and propoxyphene napsylate in patients with postpartum uterine cramping. Toxicol Appl Pharmacol 1971;19:519-27.
5.	Sunshine A, Laska E, Slafta J, Fleischman E. A comparative analgesia study of propoxyphene hydrochloride, propoxyphene napsylate, and placebo. Toxicol Appl Pharmacol 1971; 19:512-18.
6.	Deroisy R, Zartarian M, Meurmans L, Nelissenne N, Micheletti MC, Albert A et al. Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of five currently available calcium salts in healthy male volunteers. Clin Rheumatol 1997;16:249-53.
7.	Bjorn H, Hennessy DR, Friis C. The kinetic disposition of pyrantel citrate and pamoate and their efficacy against pyrantel-resistant Oesophagostomum dentatum in pigs. Int J Parasitol 1996;26:1375-80.
8.	Everett RM, Descotes G, Rollin M, Greener Y, Bradford JC, Benziger DP et al. Nephrotoxicity of pravadoline maleate (WIN 48098-6) in dogs: evidence of maleic acid-induced acute tubular necrosis. Fundam Appl Toxicol 1993;21:59-65.
9.	Emmerson JL, Gibson WR, Anderson RC. Acute toxicity of propoxyphene salts. Toxicol Appl Pharmacol 1971;19:445-51.
10.	Olovson S-G, Havu N, Regardh C-G, Sandberg A. Oesophageal ulcerations and plasma levels of different alprenolol salts: potential implications for the clinic. Acta Pharmacol Toxicol 1986;58:55-60.
11.	Altamura AC, Gomeni R, Sacchetti E, Smeraldi E. Plasma and intracellular kinetics of lithium after oral administration of various lithium salts. Eur J Clin Pharmacol 1977;12:59-63.
12.	von Oettingen WF. The aliphatic acids and their esters: toxicity and potential dangers. AMA Arch Ind Health 1959;20:59-65.
13.	Gould PL. Salt selection for basic drugs. Int J Pharm 1986; 33:201-17.
14.	Walkling WD, Reynolds BE, Fegely BJ, Janicki CA. Xilobam: effect of salt form on pharmaceutical properties. Drug Dev Ind Pharm 1983;9:809-19.
15.	Neville GA, Ethier JC. Characterization of some lincomycin and cyclamate salts by thermal analysis and infrared spectroscopy. J Assoc Off Anal Chem 1971;54:1200-10.
16.	Buckwalter FH. Antibiotic formulations. J Am Pharm Assoc Prac Ed 1954;15:694-700.

Glynis Davies is a pharmacist and medical writer. Correspondence to 19 Llys Preswylfa, Mold, Clwyd CH7 1UP

Back to Top

Citation: The Pharmaceutical Journal, March 2001, online | URI: 20004115