CV247 is under investigation and its safety and efficacy have not yet been demonstrated

SODIUM SALICYLATE

Background

The properties of the salicylates have been known for centuries, and, by the end of the C19th, salts of salicylic acid were being used to remedy the aches and pains associated with rheumatic fever. Acetyl salicylic acid was synthesised from salicylic acid in 1899 and the analgesic, antipyretic and anti-inflammatory properties of this newly synthesised “aspirin” were quickly recognised, making it the first of the non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin is a widely used drug which, like the salicylic acid salts, is rapidly hydrolysed to salicylic acid (SA) after administration both in animals and man. It is likely, therefore, that the therapeutic effects of aspirin itself are confined to the pre-systemic portal circulation, whilst the effects in peripheral tissues are due to conversion to SA. Problems associated with the use of aspirin and salicylic acid such as poor water solubility and gastrointestinal side effects have been the reason for the synthesis of different derivatives. To increase solubility, salts of salicylic acid including sodium, potassium and magnesium salts were synthesised, and are effectively pro-drugs of SA that allow for 100% bioavailability of the active compound after oral administration of the salt in solution in man. Early observations in both the rat and man found that sodium salicylate (SS) produced far less gastrointestinal irritation than aspirin (Leonards, 1973), though this has not been observed following intravenous administration in rats where similar lesions were seen (Rowe, 1987). Studies in man have found that an oral dose of 250mg SS gives plasma SA levels similar to those obtained with 320mg oral aspirin (Cerletti, 1984).

SS is monographed in several pharmacopoeias including Europe, Japan and the USA, as well as BP Vet, as an anti-inflammatory drug. The usual oral dose for pain or fever, in human adults, is 325 to 650 mg every 4 hours. It has been used in musculoskeletal and joint disorders in divided doses up to 5.4g daily. Proprietary medicines containing SS include Fennings Mixture, Jacksons Febrifuge, and Rhumax. It is also included in a variety of multi-ingredient preparations (Martindale, 1993), and is used as a denaturant and preservative in cosmetic formulations at concentrations up to 2% (cosmetic panel, 2003).

Drug interactions

SA is a substrate of the liver cytochrome P450 enzyme CYP2E1 (Wu, 2001) and this binding characteristic is the reason for interaction with other highly protein bound drugs. For example the co-administration of SA with other NSAIDs, such as diclofenac, flurbiprofen, ibuprofen and naproxen, leads to these drugs being displaced by SA often resulting in an increased total plasma clearance and in the incidence of side effects. Concentrations of both fenoprofen and indomethacin were significantly reduced when administered with SA (Rubin, 1973).

Protein binding displacement may also be the consequence of interaction with other drugs which are extensively bound to plasma proteins. Such drugs include acetazolamide, methotrexate, penicillin, phenytoin, salicylamide, secobarbital, valproic acid and warfarin (Kurowski, 1992). The salicylates should only be co-administered with anti-coagulant drugs with caution, the pharmacodynamic effect of coumarins will be increased by protein binding displacement and the bleeding tendency is potentiated by the drug itself.
The role of salicylates

The role of the salicylates in the treatment of various disease states has been widely researched. Aspirin, in particular, is a commonly used drug with a wide pharmacological spectrum. The use of SS, may include the treatment of ischaemic heart disease via inhibition of endothelin A receptors, as it has been shown in both isolated rat and human mammary arteries that SS reverses the contractile actions of endothelin-1 (Talbodec, 2000).

The transcription factor, nuclear factor (NK) kappa B is critical for the inducible expression of multiple cellular and viral genes involved in inflammation and infection, including IL-1, IL-6 and adhesion molecules. Both SS and aspirin inhibit the activation of NF Kappa B and also NF Kappa B dependant transcription from the Ig kappa enhancer and the HIV long terminal repeat in transfected T cells (Kopp, 1995).

These effects of SS and other NSAIDs are independent of cyclo-oxygenase activity and prostaglandin synthesis activity (Tegeder, 2001). However, salicylates, have been demonstrated in almost every model to exert an anti-inflammatory effect, and specifically the blocking of prostanoid synthesis from arachidonic acid by inhibition of the cyclo-oxygenase (COX) enzymes, though SA per se may predominantly affect the metabolism of arachidonate via the lipoxygenase pathway by inhibiting the conversion of 12-hydroperoxy- to 12-hydroxy-5,8,10,14 eicosatetraenoic acid. Aspirin is a potent inhibitor of COX enzymes, indeed rather more so than SA in vitro, though their anti-inflammatory potency is similar and both drugs cause a dose dependant reduction in the concentration of PGE2 in experimental inflammation. When one considers that following aspirin administration, SA concentrations in inflammatory exudates are 50 times higher than aspirin, the indications are that at least some of the anti-inflammatory activity of aspirin is through the inhibition of prostaglandin synthesis by SA and that aspirin, like SS, serves as a pro-drug for SA (Higgs, 1992). SS is a weak inhibitor of platelet aggregation in vitro, being some 100 times less active than aspirin on a concentration basis at least with regard to second phase ADP induced aggregation (Mills, 1974). However it has been reported that SA can prevent the inhibitory effects of aspirin on platelet COX activity. A group of 6 healthy volunteers received oral doses of 250mg and 1000mg SS. The platelet aggregation and thromboxane B2 generation inhibitory effect of subsequent intravenous dosing with 40mg aspirin was only significantly prevented in the group pre-treated with the 1000mg SS dose and hence would seem to be dose dependant (Cerletti, 1984). Two COX genes have been cloned, COX 1 and COX 2 which although have similar enzymic activities are different in the regulation of their expression. Expression of COX 1 is not usually regulated whilst COX 2 is low or undetectable in most tissues, but is induced in response to cell activation by pro-inflammatory cytokines, growth factors and tumour promotor. Consequently COX 2 has a pathophysiological role connected to inflammation and carcinogenesis.

Recent interest in the NSAIDs, in general, has been a possible role as chemotherapeutic agents. The use of aspirin per se has been associated epidemiologically with a 50% decrease in the incidence of colon cancer in man (Potter, 1999) and has been associated with reduced incidence of both cancer of the oesophagus and stomach (Farrow, 1998) and possibly with that of the lung and breast cancers (Schreinemachers, 1994), though a multi-centre case control study in prostate cancer conducted in Italy did not support a protective role of regular aspirin use (Bosetti, 2006). The ability of such NSAIDs to induce tumour regression is possibly via induction of apoptosis, and inhibition of angiogenesis resulting in prevention of tumour growth by anoxia. Both COX selective and nonselective NSAIDs inhibit angiogenesis through direct effects on epithelial cells
involving inhibition of mitogen activated protein (MAP) kinase (ERK2) activity (Jones, 1999). Apoptosis is mediated by a family of cysteine proteases termed caspaces that cause cell death by degrading critical cell structures such as lamins and gelsolin. The cytotoxic activity of SS has been measured in HL-60 cells after exposure of increasing concentrations from 0.5 to 7 mmol/L for 24 hr. Mean cell viability gradually dropped in a dose dependant manner. After incubation with the IC50 dose of 5mmolSS/L, cells displayed clear signs of apoptosis which appeared to be dependant upon caspase 8 activation (Chen, 2002). Curiously, even though aspirin inhibits both COX enzymes, it was found not to induce apoptosis in human colorectal HT-29 cell lines (Qiao, 1998). COX 2 has been found to be over-expressed in a variety of epithelially derived tumours, including carcinoma of the pancreas, gastric carcinoma, lung cancers (specifically adenocarcinomas) and prostate adenocarcinoma. The proposed mechanisms of the anti-neoplastic effects of NSAIDs via the inhibition of COX-2, which could result in both apoptosis and inhibition of angiogenesis, may be several:

1. Inhibition of COX 2 could result in the inability of the cell to live because of depletion of a COX 2 generated survival factor that could act on the neoplastic cell in an autocrine fashion.
2. Tumour cells could undergo apoptosis due to anoxia induced by destruction of the tumour vasculature. It has been demonstrated that elevated levels of PGE2 synthesised in tumour cells over-expressing COX-2 result in secretion of VEGF, and TGFβ which, amongst others, induce angiogenesis. Thus COX 2 inhibition would be anti-angiogenic.
3. PGE2 has several inhibitory effects on lymphocytes including suppressing lymphokine activated killer cells and cell-cell mediated tumour cell killing. Since the majority of PGE2 secreted by tumour cells appears to be the product of COX 2, inhibition of COX 2 could stimulate anti-tumour immunosurveillance (Simmons, 2001).

The COX 2 tumour hypothesis has been supported by various experimental animal models but does not preclude the role of other factors, such as the role that COX 1 plays in carcinogenesis, and the fact that SS prevents nuclear factor kappa B activation and can cause apoptosis (Wu, 2001). In addition, expression of COX 1 and/or COX 2 by the tumour stroma (connective tissue cells, inflammatory cells and vascular endothelium) may contribute to tumourigenesis. Salicylates are weak inhibitors of both isolated COX 1 and COX 2 but are potent inhibitors of prostaglandin (PG) synthesis in intact cells. At low concentrations of arachidonic acid, COX 2 is the major isoenzyme involved in PGE2 synthesis and salicylate, or its metabolites, may selectively inhibit PGE2 synthesis involving COX 2 because the lower flux through this pathway produces less levels of the hydroperoxide PGG2 than the pathway involving COX 1 (Graham, 2003).

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics of sodium salicylate in man**

The absolute bioavailability of SS was found to be 100% after oral administration of a solution in a dose of 9mg/kg to normal male and female subjects. There were sex differences with regard to tmax (it reaching its nadir in the middle of the menstrual cycle when gastric emptying is at its shortest), but not the Cmax of SA which was reached after 32 and 54 min in males and females respectively. There were no differences with regard to apparent volume of distribution, plasma clearance, or AUC (Miaskiewicz, 1982).
Following orally administered doses of 250 and 1000g SS to 6 healthy volunteers, the mean peak plasma concentrations of SA were observed to be 20 and 76 microg/ml respectively (Cerletti, 1984).

Single dose SS pharmacokinetics have been examined in a study to evaluate its efficacy as an analgesic for post operative dental pain. SS at 537mg and 1074mg were compared in a cross over study in 24 patients. Peak plasma concentrations of SA were observed 30 minutes after oral dosage following the lower dose, but after 45 minutes in the higher dose group (Seymour, 1984).

The pharmacokinetics of salicylate after a single oral dose of 600mg of SS have also been investigated in 22 male subjects, in which it was found that the urinary recovery of SA and its metabolites essentially accounts for all the administered dose and was not influenced by age, nor was the apparent oral clearance of SA. An increase in the apparent volume of distribution and a decrease in the Cmax and renal clearance of SA, with increasing age was observed, the latter correlating with creatinine clearance. Overall, however the authors concluded that age does not have a major influence on salicylate disposition in man (Abdallah, 1991). Another study in 28 subjects who received single oral doses of 1g SS observed that AUCinf did not correlate with age and nor was there any gender difference. Clearance was only affected by serum albumin concentrations a reduction in which, as may be seen with increasing age, decreased serum protein binding resulting in slower elimination of salicylate (Netter, 1985).

**Absorption, Distribution, Metabolism and Excretion in man**

**Distribution**

After absorption SA shows a concentration dependant plasma protein binding. At low concentration about 90% is bound, but at higher (toxic) levels of 400microg/ml only about 76% is bound (Dromgoole, 1981). Since only unbound drug is available for distribution, an increase in this free drug leads to an increase in the volume of distribution. In addition protein binding is influenced by pH and changes in the protein concentration in plasma. For example a decrease in the plasma protein concentration of 5g to 2g/100ml leads to an increase in unbound salicylate from 10% to 50%.

It has been shown that high concentrations of absorbed SS are found in vivo in the glandular region of the stomach, in kidney tubules and in inflamed tissues. In vitro studies using human erythrocytes suspended in buffer of different pH, showed that added SS accumulated in these cells when the pH was reduced from 7.4-6.8. Since SA is a weak acid it is likely to accumulate within cells which are surrounded by bordering acidic fluids, as is the case in the stomach, kidney and inflamed tissues (Brune, 1977). The ionised form of salicylate is significantly taken up into human red blood cells, a mechanism that may involve the membrane protein fraction (Nishihata, 1984).

**Metabolism**

SA is metabolised by linear and saturable processes. It may be conjugated with glucuronic acid to form acyl or phenolic glucuronides, or with glycine to form salicyluric acid (salicylglycine, o-hydroxyhippurate). In addition hydroxylation leads to the formation of 2,3 dihydroxybenzoic acid and gentisic acid (2,5 dihydroxybenzoic acid) which in turn is either eliminated or conjugated with glycine to form gentisuric acid. Experiments with anti-oxidant inhibitors indicate that superoxide dismutase, haem
protein inhibitors and glutathione block gentisic acid formation (Davis, 1989). The formation of salicyluric acid is the preferred metabolic pathway, but the capacity for the formation of both this and salicyl phenolic glucuronide is limited leading to an increase in the elimination of the other metabolites if the concentration of SA in the body exceeds 600mg. The overall elimination of salicylate proceeds by first order kinetics at low doses and by both zero and first order kinetics at higher doses. Consequently the elimination plasma half life increases with dose, and plasma concentrations increase disproportionately which is most pronounced with respect to unbound plasma SA due to decreased protein binding (Levy, 1980). Such capacity limited metabolism has been shown to increase the half life of SA from about 3.5hr to over 30hr. This non linearity in SA metabolism is of importance with long term, high dose therapy with salicylates, though it has been observed that SA is likely to induce its own metabolism associated with a decrease in plasma levels and an increase in the urinary elimination of salicyluric acid by approximately 50% after 3 days of treatment (Dromgoole, 1981).

Excretion

The influence of intavenous SS on renal function has been investigated in a cross over study in a group of 6 healthy female volunteers. Following a bolus injection of 0.444g, or a continuous infusion of 1.332g or placebo over 170 minutes, urine and plasma samples were collected for the following 3 hour period. Plasma SA levels were between 22.5 and 108.9 microg/ml during SS infusion. There was no change in urine volume or renal clearance of sodium, potassium, creatinine or inulin, nor any change to osmolarity when compared with placebo. Renal prostaglandin synthesis which is suppressed by acetyl salicylic acid, was not affected by SS (Reimann, 1985). SA and its metabolites are mainly eliminated by urinary excretion, though renal elimination is strongly pH dependant. Raising the pH leads to an increase in the excretion of SA per se as only unionised molecules can be re-absorbed. For example when sodium hydroxide, or even magnesium hydroxide combination antacid, is added with a dosing regimen of aspirin such that urinary pH is raised by 1 unit, steady state SA concentrations are decreased by about 40% (Furst, 1988). The fact that alkaline urine increases the renal clearance of SA is common to many animal species (Roch-Ramel, 1979).