Appendix 8
3

AXSAIN CREAM 0.075%

Combined Pharmacological/Toxicological and Clinical Expert Report

Toxicology

Capsicum (BPC, 1973) consists of the dried ripe fruits of Capsicum annum var. minimum (Miller) Heiser and small-fruited varieties of C. fruitescens L. (Fam. Solanaceae). Capsicum contains 0.5 - 0.9 % of the colourless, crystalline pungent principle, capsaicin which melts at about 65° and is volatile at higher temperatures, the vapour being extremely irritating (1).

Capsaicin, usually as the tincture, is given by mouth as a carminative. It is used externally as a counter-irritant for the treatment of rheumatism, lumbago and neuralgia (1).

The safety and efficacy of topical capsicum preparations (capsaicin, capsicum and capsicum oleoresin) have been reviewed by the FDA's OTC external analgesics panel (FR, Vol. 44 No. 234, 4 December 1979) (2) and were found to be safe and effective when applied to adults and children over two years of age at a concentration of 0.025 - 0.25% capsaicin not more than 3 - 4 times daily. The safety review shows that capsaicin produces erythema and a burning sensation without vesication when applied to human skin. There is a pronounced irritant effect on the ending of sensory nerves, but little action on capillary or other blood vessels, therefore it is not associated with blistering.

The safety of capsaicin-containing products is well documented by marketing data. The FDA review (2) states that one product containing capsicum has sold more than 38,500,000 units and another in excess of 22,300,000 units during the period 1960-1972. Another manufacture reported annual sales of greater than 500,000 packages/year. These manufacturers reported a total of 16 customer complaints, with none being of a serious nature.

More recently there have been some reports of possible mutagenicity or carcinogenicity of chilli extract or capsaicin (3,4,5,6). In 1984 Toth and Rogan (3) examined the mutagenicity of capsaicin in the Ames test. Mutagenic activity was only observed in strain TA 98 in the presence of arochlor-induced rat liver activating enzymes. The source or purity of capsaicin used in this study was not reported. The study itself was a preliminary study and has not been followed by a definitive publication.

In 1985 Nagabhushan and Bhide (4) tested vanillin, capsaicin and chilli extracts for mutagenicity in Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538. Vanillin was non-mutagenic, whereas chilli extract and capsaicin were mutagenic in the presence of metabolic activation (arochlor-induced rat liver activating enzymes). Capsaicin was the more potent mutagen. However, work by Buchmann et al (5) reported that capsaicin and chilli extract were non-mutagenic in Salmonella. In these studies Buchmann used microsomes from phenobarbital-induced rats.

Chilli extract and capsaicin were also tested by Nagabhushan and Bhide (4) in the micronucleus test and the 8-azoguananine-resistant mutagenicity assay in V79 Chinese hamster cells. Both the chilli extract and capsaicin were negative in the V79 cells, whereas in the micronucleus test, capsaicin was positive near the LD50 dose.

Toth and Rogan (3) treated five groups of Swiss mice, four males and four females per group, with capsaicin in the diet (1, 0.5, 0.25, 0.125 and 0.06325%) for 35 days. Four mice (10%) developed four adenocarcinomas of the duodenum at 72, 91, 100 and 126 weeks of age, one tumour at each dose level, except the top dose level. No such tumours were found in the corresponding untreated controls (100 males plus 100 females).

In contrast, work by Modly et al (6) demonstrated that capsaicin has potent anti-carcinogenic effects. In this study capsaicin inhibited human and murine epidermal metabolism of benzo (a) pyrene and the enzyme-medicated binding of benzo (a) pyrene metabolites to DNA.

Thus, some poorly documented reports of possible mutagenicity/carcinogenicity of chilli extract or capsaicin have been noted. Other published reports of similar or more extensive studies have shown either no such adverse effects or indeed anti-carcinogenic effects of capsaicin. None of the studies, with the exception of the Modly study (6) has any relevance to capsaicin's use on the skin and the safety of 0.075% capsaicin in Axsain is felt to be well established by the FDA review (2). (References 3-6 are included in Annex III).

Pharmacology

Over the last 20 years, a number of peptides have been identified in neurons of the brain, spinal cord and peripheral nerves which are thought to transfer nerve impulses from one neuron to another or to an unrelated effector cell. Within recent years, some of these neuropeptides have been recognised as playing important roles in the skin. One such peptide, Substance P (SP) is localized in cell bodies and nerve terminals in the peripheral nervous system in the skin, and has been shown to be an important chemotransmitter of pain from the periphery to the central nervous system (7-11). Numerous experiments have demonstrated SP release in response to noxious stimuli with resulting pain and the inhibition of certain types of pain sensation with agents locally depleting SP (12-14).

In the 1960's Jansco and co-workers demonstrated that topical capsaicin renders human and animal skin insensitive to various types of chemical pain stimuli (15,16). More recently it has been shown that local application of capsaicin results in the depletion of SP (17-19).

Axsain cream contains 0.075% capsaicin and is indicated for the relief of pain associated with and following herpes zoster infections once the blisters have healed, and for the painful peripheral neuropathy associated with diabetes.

In most studies of capsaicin's pharmacology its metabolic profile has not been studied (20) and absorption after topical application is not currently known. Average consumption of dietary spice from capsicum fruit has been estimated as 2.5 g/person/day in India and 5.0 g/person/day in Thailand. Capsaicin content in capsicum fruit is approximately 1% and therefore daily dietary intake of capsaicin may range from 0.5-1.0 mg/kg/day for a 50kg person (21). Application of two tubes of Axsain Cream (90 grams) each week results in 9.6 mg/day from dermal exposure. Assuming 100% absorption in a 50kg person, daily exposure would be 0.192 mg/kg, approximately a third to a quarter of the above mentioned dietary intake.

Clinical Studies

Introduction:

Severe pain may accompany the vesicobullous stage of herpes zoster and especially in the elderly, may continue after healing of the skin lesions. In such older individuals severe pain is common and tends to be intractable and exhausting. There are few treatments utilized for post-herpetic neuralgia that offer any measurable clinical benefit; the response rates with most currently employed treatment regimens are not significantly different from those with placebo.

Similarly, peripheral neuropathy is a common complication of diabetes and the associated pain, described as burning, stabbing or tearing in character, may be disabling. It has been difficult to target specific therapy for this problem as the mechanistic basis of the pain has yet to be determined. Current approaches have some degree of efficacy but side effects can limit use of eg anticonvulsants or amitryptiline.

In this application three trials using Axsain cream are reported. All were randomised and double blind against placebo (cream base with no capsaicin). One of the trials was subsequently immediately extended into a long term open phase. A total of 221 patients entered the trials, 114 received Axsain cream 0.075% and 107 placebo.

Efficacy

In the first two trials reported, patients had a history of severe intractable post-herpetic neuralgia of at least 6 months' duration. Axsain cream or placebo was applied to the affected area 3-4 times daily for six weeks, with assessment at 2, 4 and 6 weeks. In the long term open extension to the second trial, 83 patients applied cream 4 times daily for varying periods up to two years, with assessments at eight week intervals after the first six weeks. Intensity and relief of pain were subjectively assessed by the patient using a categorical scale (none, slight, moderate, severe and very severe) and visual analogue scales, with a physician's global evaluation at each visit.

32 patients were enrolled in the first study (Bernstein et al), sixteen in each treatment group. Three patients failed to complete the 6-week trial. The two groups were compared using the students t-test, chi-square analysis, Fisher's Exact test and the Mann-Whitney test. The results confirmed the greater efficacy of Axsain cream compared to placebo for all variables tested.

Results after 6 weeks

	Axsain Cream	Placebo	Statistical Significance
Physician's Global Rating	77% of patients had reduction in pain	31% of patients had reduction in pain	$p < 0.05$
Categorical pain scale	46% of patients reported pain relief	6% of patients reported pain relief	$p < 0.01$
Visual analogue scale (severity)	30% mean decrease from initial pain score	1% mean increase in pain score	$p < 0.05$
Visual analogue scale (relief)	54% of patients experienced relief	6% of patients experienced relief	$p < 0.02$

Though the results given above are for six weeks of treatment, significant clinical benefits were noted after two weeks, with 62% of capsaicin-treated patients versus 31% of placebo-treated patients rated as improved ($p < 0.05$), and similar significant differences on all the patient assessed scales. In general, the actual degree of efficacy as assessed by the physician's global rating was not obvious from the results given as all improvement categories were combined. However, the results on the visual analogue scores suggest a good degree of efficacy with eg 54% of patients reporting 40% or more pain relief after six weeks' capsaicin treatment (see table above).

The second study (Ramamurthy et al) involved 143 patients, 74 of whom were treated with Axsain cream and 69 with placebo. 12 patients did not fully meet all protocol entrance requirements and a further 6 violated protocol during the study, leaving 125 patients to be included in the efficacy analysis. In addition to the pain variables, the effect of pain on the patients' capacity to perform various daily functions such as eating, sleeping, bathing was assessed. Treatment groups were compared using students's t-test, Fisher's exact test, Wilcoxon two sample test and Cochran-Mantel-Haenszell analysis. Two separate efficacy analyses were carried out, one to include all patients and one separating out these with post-herpetic neuralgia of more than 12 months' duration (n=93). Axsain cream was found to be significantly more effective than placebo in both analyses for all efficacy variables, with more dramatic differences in the latter group.

Results after 6 weeks

All patients

	Axsain Cream	Placebo	Statistical Significance
Physician's Global Rating	63% of patients had reduction in pain	34% of patients had reduction in pain	$p < 0.05$
Categorical pain scale	38% of patients reported pain relief	20% of patients reported pain relief	$p < 0.015$
Visual analogue scale (severity)	20.9% mean decrease from initial pain score	5.8% mean increase in pain score	$p \leq 0.03$

Results after 6 weeks

Patients with post-herpetic neuralgia exceeding 12 months in duration

	Axsain Cream	Placebo	Statistical Significance
Physician's Global Rating	64% of patients had reduction in pain	25% of patients had reduction in pain	$p \leq 0.01$
Categorical pain scale	39% of patients reported pain relief	6% of patients reported pain relief	$p \leq 0.006$
Visual analogue scale (severity)	15% mean decrease from initial pain score	5.2% mean increase in pain score	$p \leq 0.03$
Visual analogue scale (relief)	Nearly 100% greater reduction for Axsain compared with placeo		$p < 0.02$

Analysis of functional capacity revealed greater improvement as a result of capsaicin treatment, but the differences, though substantial, were not generally statistically significant, with the exception of eating ($p < 0.05$) in the overall efficacy analysis.

Though the results given above are from the final assessment visit, significant clinical benefits of Axsain treatment were noted after two weeks for all efficacy variables. Again the degree ofimprovement was not obvious from the physician's global evaluation as all categories were combined. However, results on the visual analogue scales suggest good efficacy of Axsain, and considerable superiority as compared with placebo.

A greater placebo effect was noted in the efficacy analysis of all patients compared with that observed for patients with post-herpetic neuralgia exceeding 12 months in duration. This finding is not unexpected as post-herpetic neuralgia does tend to resolve spontaneously with time, and of 100 patients with the condition only 2 to 3 will continue to suffer with severe pain one year after the acute herpes episode (22).

83 patients entered the open long term phase of the trial, 44 previously treated with Axsain and 39 with placebo during the double-blinded phase. Patients were treated for up to two years, mean duration of treatment was 140 days with a range of 43-708 days. Post-herpetic neuralgia was improved in 65% of 77 patients treated for more than 6 weeks and in 71% of 52 patients treated for more than 12 weeks. Using a baseline of 6 weeks' treatment to assess the value of long term treatment, the condition was further improved in 36% of patients, stabilised in 50% and had deteriorated in 14% of patients at the last long term visit. Of the 63% of patients rated as improved after 6 weeks double-blinded capsaicin treatment, 79% either maintained this improvement (52%) or were further improved (27%). Of those, 33% rated as not improved, 43% improved with further treatment, with no change in condition of the 4% of patients rated as worse after 6 weeks' double-blinded treatment.

In the third study, 46 of an initial 58 patients with a history of painful peripheral neuropathy associated with stable and well controlled diabetes completed treatment with Axsain cream (n=24) or placebo (n=22), topically applied to the affected areas 4 times daily for 4 weeks. Assessments were made at 2 and 4 weeks, of pain on categorical (none, slight, moderate, severe and very severe) and visual analogue scales by the patient, with a physician's global evaluation of response to therapy. 5 trial centres were involved. Eight patients withdrew prematurely, 2 had severe painful radiculopathy and in 2 others the cause of the neuropathy was doubtful, having preceded the diabetes by more than 7 years.

The treatment groups were compared using logistic regression analysis of improved versus unimproved patients and analysis of variance. The results point to, but do not establish, a possible effect of topical capsaicin administration on painful diabetic polyneuropathy.

Results after 4 weeks

	Axsain Cream	Placebo	Statistical Significance
Physician's Global Rating	71% of patients had reduction in pain	50% of patients had reduction in pain	n.s.
Categorical pain scale	67% of patients reported pain relief	46% of patients reported pain relief	n.s.
Visual analogue scale (severity) % patients improved by 10 more more points	71%	46%	n.s.
Visual analogue scale (relief) % patients relieved by 20% or more	71%	41%	$p < 0.05$

The investigators noted that the capsaicin effect was most evident in four of the five centres studies. In the other centre capsaicin was shown to be ineffective, with patients responding excellently to vehicle. The company has informed us that six paitents were involved, three treated with capsaicin and three with vehicle. Full patient data is supplied. Capsaicin was shown to be significantly effective in reducing pain severity on the visual analogue scale ($p < 0.05$) in patients with painful neuropathy exceeding 4 years in duration, while patients with pain of less than 3 years' duration or less experienced relief irrespective of treatment used.

Safety

A mild to moderate burning sensation was reported in 53 patients treated with Axsain cream and 27 of those treated with placebo. In most cases, reactions predominated in the first week of treatment and subsequently disappeared. Only 1 Axsain-treated patient and 1 vehicle-treated patient reported severe burning. Of the 83 patients treated for up to 2 years in the long term phase of the second study, only 7 (9%) reported burning or stinging. In the third study, 1 Axsain-treated patient experienced hyperalgesia of the feet and one vehicle-treated patient had pruritis which resolved spontaneously after 10 days.

As reported by the FDA's OTC external analgesics panel (2), capsaicin is known to produce erythema and burning when applied to human skin, and therefore the reported incidence of burning is not unexpected.

Conclusions

The trials, based on subjective assessment of pain, confirm the efficacy of Axsain in the treatment of post-herpetic neuralgia with significant superiority as compared to placebo. Previous experience with topically applied capsaicin has demonstrated a short duration of action (23) and therefore it is necessary to apply the drug three to four times daily to maintain pain relief.

Significant clinical benefit may be obtained after two weeks' treatment, and long term results show that improvement gained after six weeks' treatment is maintained or amplified with longer durations of therapy. Few adverse effects of either short or long term use were noted other than localized burning or erythema on initial application, possibly ascribable to the release of existing stores of substance P from peripheral sensory neurons into the skin (23) and thus directly related to the pharmacological actions of the drug. The cream was therefore shown to be safe and efficacious for short or long term use in the relief of pain associated with post-herpetic neuralgia.

The results of the trial of efficacy of Axsain in painful diabetic polyneuropathy were not conclusive, owing to the relatively small numbers of patients involved, high placebo effect and an obvious centre/investigator effect. However, with further study, capsaicin might prove to be a novel and potentially useful approach to the management of painful diabetic polyneuropathy.

It is acknowleged that the number of documented reports of treatment with Axsain cream is small. However, the efficacy of capsaicin as a topical analgesic at concentrations of 0.025-0.25% is well supported by the findings of the FDA OTC external analgesics panel. Therefore I am of the opinion that Axsain cream contining 0.075% capsaicin is a safe and effective treatment for the temporary relief of pain associated with post-herpetic neuralgia, and painful diabetic polyneuropathy.

Signed: [redacted] .... Date: [redacted]

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Copies of the references are available on request.