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Analgesic activity of anticancer agent suramin

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Suramin exhibited morphine-like analgesic activity in mice. It antagonized both thermal (hot-plate) and acetic acid-evoked writhing responses with ED_{50} values 1/100 and 1/68, respectively, that of morphine. The suramin- and morphine-induced hot-plate analgesia was suppressed by administration of 0.5 mg/kg naloxone. However, lower doses (5–30 μg/kg) of naloxone produced dose-related potentiation or suppression of suramin and morphine analgesia. This potentiation effect may be due to the inhibition of writhing by naloxone itself rather than be a direct antagonism of the morphine effect.

Key words: Analgesic activity, morphine, naloxone, suramin.

Introduction

Suramin, the trisodium salt of a polysulfonated napthylurea 8, 8′-[*O,O′*-ureylene-bis(*O′*-benzamido-*p′*-methylbenzamido)]-bis-1,3,5-napthylenetrisulfonic acid, was the first widely accepted antiparasitic agent developed and is still one of the most commonly prescribed antitrypanosomal drugs. Recently, several new pharmacologic features of suramin have been discovered. For example, suramin has been shown to inhibit reverse transcriptase in human immunodeficiency virus (HIV)-infected cells *in vitro*,[1] to reduce the *in vitro* infectivity of human T cell leukemia virus (HTLV)-III virus,[2] and to block the stimulatory effect of a number of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β and epidermal growth factor (EGF) on certain tumor cells *in vitro*.[3,4] Phase I trials of suramin have recently been conducted in patients with AIDS and those with cancer, and responses have been noted against Kaposi's sarcoma,[5] lymphoma, adrenocortical carcinoma[6–8] and advanced prostate carcinoma.[9–11] During the course of a phase I trial of suramin at The University of Texas MD Anderson Cancer Center, patients experienced decreased pain sensation, which appeared to be drug related. This observation prompted us to undertake assessment of the analgesic properties of suramin in rodents.

Material and Methods

Hot-plate test

Groups of 10 male ICR mice (20–25 g; Charles River, Wilmington, MA) were used. Analgesic responses were measured on an UGO Basile Hot-Plate (Model DS 37; Stoelting, Chicago, IL) maintained at 55°C. The latency between the time an animal was placed on the surface and the time it licked either of its hindpaws or escaped by jumping off the plastic cover was recorded. Failure to respond in 60 s resulted in termination of the trial.

Varying doses of morphine sulfate and suramin sulfonate (supplied by National Cancer Institute, Bethesda, MD) were injected i.p. 30 min prior to a test. Analgesic activity was expressed as the percent analgesia, computed by comparing the difference of mean response times between the drug and saline control groups. Potencies were compared between ED_{50} values (i.e. the dose that produced 50% analgesic activity) obtained from the dose–response curves, using computer-generated least square plots. To study the effect of naloxone on drug-induced analgesia, naloxone hydrochloride was injected s.c. into animals 10 min prior to administration of ED_{50} doses of either suramin or morphine. Control animals received saline alone instead of naloxone.

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Table 1. Comparison of analgesic activities of suramin and morphine

	Hot-plate			Writhing		
	ED_{50}[a]		Relative potency	ED_{50}[a]		Relative potency
	mg/kg	μmol/kg		mg/kg	μmol/kg	
Morphine sulfate (MW 669)	2.1	3.1	1	0.37	0.55	1
Suramin (MW 1429)	440	308	1/100	53.0	37.1	1/68

[a] The dose of compound that produced 50% analgesia.

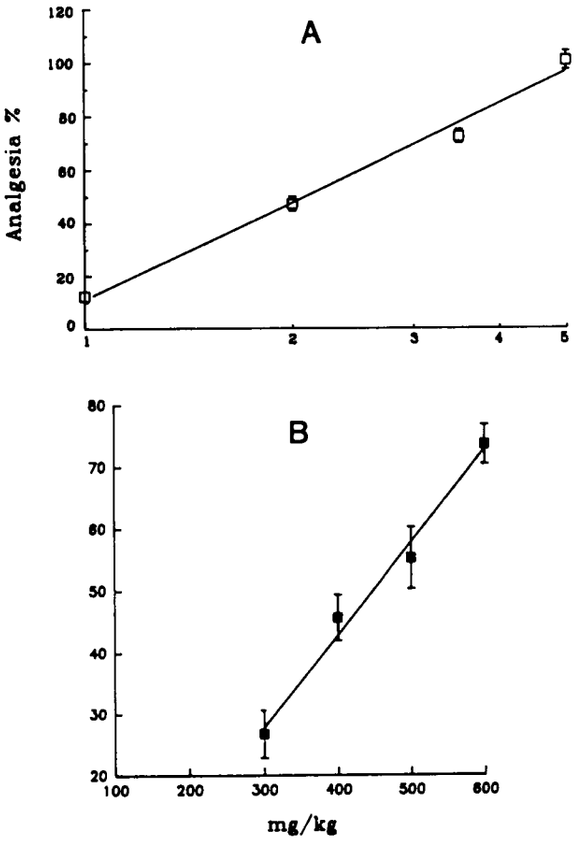

Figure 1. Dose–analgesic effect plot of (a) morphine and (b) suramin measured in the hot-plate tests.

Writhing test

Mice that show the writhing syndrome within 5 min after injection with acetic acid (0.6%; 10 ml/kg, i.p.) were used for the experiment. Animals first received varying doses of morphine sulfate or suramin sulfonate in saline; controls received saline alone. At 30 min later, they were injected with acetic acid and then the number of writhings were counted for 5 min, beginning 5 min after the acetic acid injection. Analgesic activity was expressed as the percent analgesia, computed by comparing the difference of numbers of writhings between the saline control and drug-treated groups.

Results

Suramin exhibited an analgesic property in both hot-plate and writhing tests. However, its potency in those tests was only 1/100 and 1/68, respectively, of that of morphine (Table 1, Figures 1 and 2). Both the morphine- and suramin-induced hot-plate analgesia, produced by ED_{50} doses in mice, were suppressed by a low (0.5 mg/kg) dose of naloxone (Table 2); nevertheless, the degree of suppression was greater in morphine- than in suramin-treated animals.

During the writhing experiments, when 0.5 mg/kg dose of naloxone was first used in mice receiving ED_{50} doses of morphine, this dose was found to potentiate rather than suppress analgesia measured by acetic acid-evoked writhing responses. Much lower doses (5–30 μg/kg) of naloxone were subsequently used. Figure 3 showed that doses of naloxone below 17 and 22 μg/kg suppressed the analgesic effects of morphine (Figure 3a) and suramin (Figure 3b), respectively, at their ED_{50} doses. Potentiation of morphine and suramin analgesia was also observed following doses of naloxone below the two above-mentioned doses. Though naloxone itself in the dose range 0.5–10 mg/kg was ineffective in inducing analgesia measured by the hot-plate method (data not shown), naloxone exhibited an agonist property in the writhing test, with an ED_{50} value of 25 μg/kg (or 69 pmol/kg)(Figure 2c).

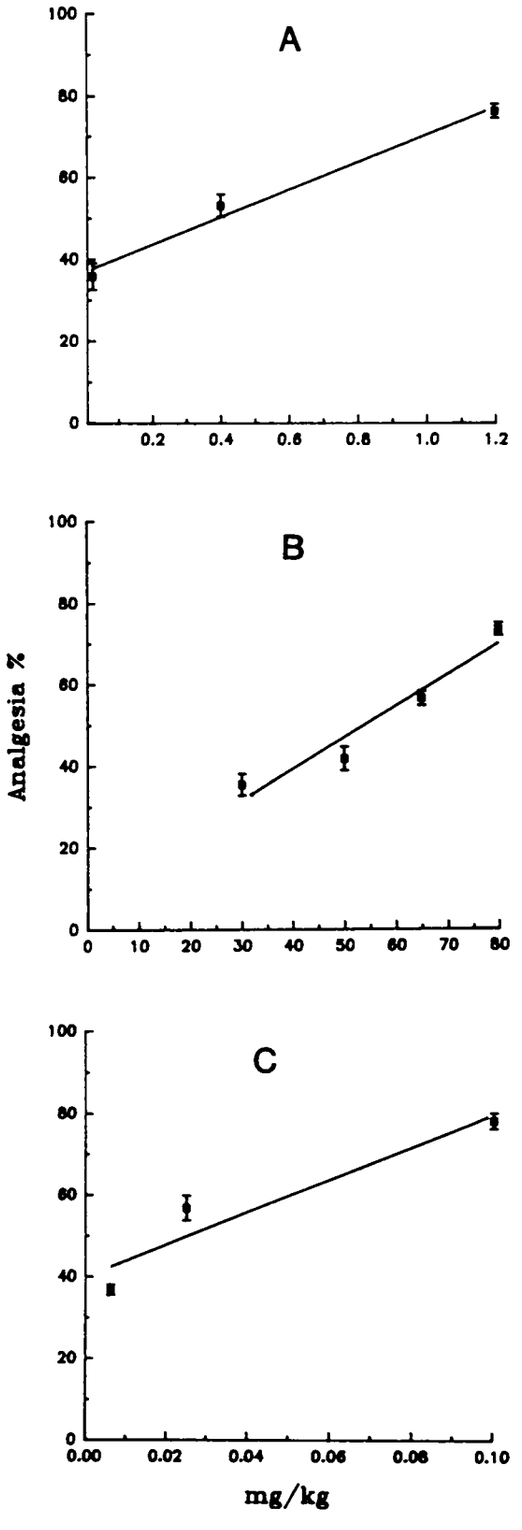

Figure 2. Dose–analgesic effect plot of (a) morphine, (b) suramin and (c) naloxone measured in the acetic acid-evoked writhing tests.

Table 2. Naloxone (0.5 mg/kg) suppression of suramin and morphine-induced hot-plate analgesia

	ED_{50} (mg/kg)	Percent analgesia	
		Without naloxone	With naloxone
Morphine	2.1	50	−14.6
Suramin	440	50	30.8

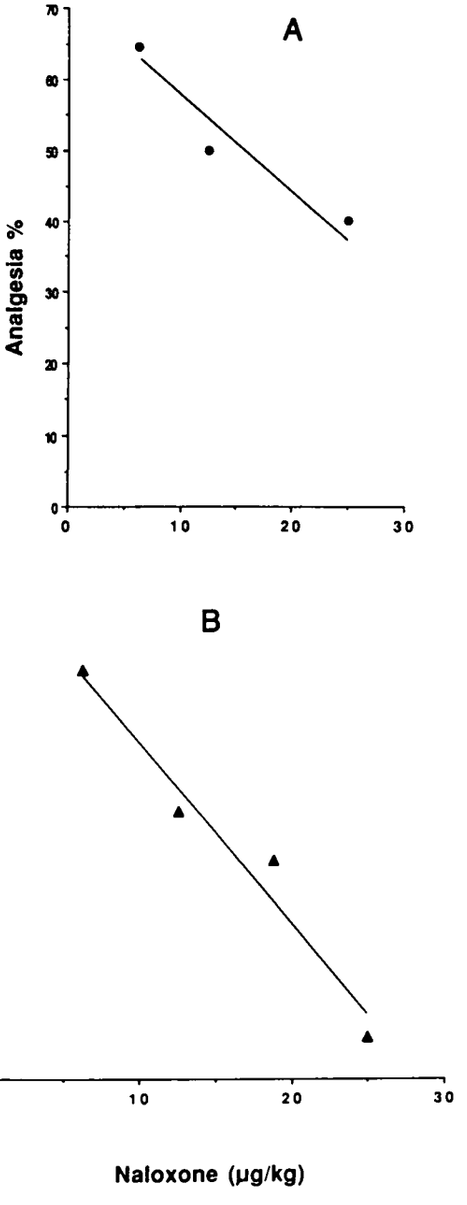

Figure 3. Effect of naloxone on the inhibition of acetic acid-evoked writhing response by ED_{50} doses of (a) morphine (2.1 mg/kg) and (b) suramin (440 mg/kg).

Discussion

Suramin, like morphine, is active in antagonizing both cutaneous thermal (hot-plate)-evoked and visceral chemical-evoked writhing responses in mice. In this aspect, our data indicate that suramin has a weaker analgesic efficacy than morphine. Studies in the past have focused on the association of various opioid receptor subtypes with cutaneous thermal and visceral stimuli. According to those reports, agents with significant μ receptor-mediated activity were able to antagonize the response evoked by cutaneous thermal and visceral chemical stimuli.[12,13] Furthermore, agents with relative δ selectivity blocked cutaneous thermal responses but were without measurable effects on visceral chemical-evoked responses, and agents with significant affinity for the κ receptor had little effect against cutaneous thermal-evoked pain even at considerably high doses.[12] Based on the above findings, it is speculated that the analgesic effect of suramin is likely mediated through the μ receptor. Further study is necessary to substantiate this conclusion.

The observed potentiation of morphine and suramin analgesia by lower doses of naloxone is unexpected. Analogous to this phenomenon Leander *et al.*[14] reported that ICI 174864, a selective δ receptor antagonist, produced additive effects on the inhibition of acetic acid-evoked writhing by threshold doses of a δ agonist LY198572. Thus, it is likely that these low doses of naloxone did not antagonize morphine and suramin and that the potentiation of morphine and suramin is merely the result of inhibition of writhing by naloxone itself.

Patients at the University of Texas MD Anderson Cancer Center received 350 mg/m^2 suramin as a continuous infusion over 34 h. Even though open to possible error, one can compare human and mouse doses assuming equivalency on the basis of mg/m^2.[15] Accordingly, we approximate that the human suramin dose is higher than the analgesic ED_{50} dose (53 mg/kg or 159 mg/m^2) against acetic acid-evoked writhing response in mice but lower than the ED_{50} dose (440 mg/kg or 1.3 g/m^2) found in mice using the hot-plate test. The dose required for producing analgesia in humans has not been reported.

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