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LETTER TO THE EDITOR

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The alkaloid sinomenine lacks efficacy in rat heart transplantation

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Sir,

In 1996 Candinas et al. [1] reported on the efficacy of sinomenine – an alkaloid extracted from the chinese plant *Sinomenium acutum* with structural similarities to morphine [3] – in rat heart allotransplantation. In the stringent strain combination of ACI(RT1^a)-to-Lewis(RT1^l) rats, the compound given at a daily dose of 15 mg/kg body weight by continuous infusion using an osmotic minipump placed intraperitoneally, together with cyclosporine given by daily intramuscular injection at 1.5 mg/kg body weight, yielded a median survival time of 46 days (range 18–54 days, $n = 5$), whereas control vehicle-treated recipients or recipients treated with sinomenine alone rejected their allograft at 5 days after transplantation. Cyclosporine given alone at 1.5 mg/kg intramuscularly showed a marginal effect, i.e., a median graft survival of 8 days. We were intrigued by this observation and performed a study aimed to reproduce these data.

The study was performed in accordance with the Swiss Animal Welfare Act dated March 9, 1978, and the accompanying Animal Welfare Regulation of May 28, 1981. Heterotopic heart transplantation was performed in the abdomen, with anastomoses between the donor aorta and the recipient infrarenal abdominal aorta and between the donor right pulmonary artery and the recipient inferior vena cava, using the stringent strain combination of male donors of the DA (RT1^a) strain and recipients of the Lewis (RT1^l) strain [2]. This was followed by daily palpation of the abdomen for a beating graft: in case of cessation of heartbeat, the experiment was terminated. The graft was subsequently taken and assessed for histologic signs of rejection, scored as marginal, slight, moderate, or severe based on the extent of mononuclear cell infiltration and damage to the myocyte parenchyma. We had previously reported that cyclosporine as microemulsion preconcentrate (Neoral; Novartis Pharma AG, Basel, Switzerland) is marginally effective at a daily oral dose of 2.5 mg/kg body weight (10–14 days graft survival, versus 7 days in controls), while it yields long-term survival (≥ 100 days) at a daily oral dose of 5 mg/kg body weight [2]. In this previous study, we had also documented synergism in combination with the immunosuppressive macrolide SDZ RAD, i.e., using suboptimal cyclosporine doses of 1.0 and 2.0 mg/kg. Since synergism with sinomenine was the aim of the present study, we used the suboptimal oral dose of 1.5 mg/kg cyclosporine given daily. Sinomenine was obtained from Aldrich Chem. Co., and converted into hydrochloride form to increase its water solubility. The compound, dissolved in distilled water, was administered by osmotic minipump (model 2002; Alzet, Palo Alto, Calif.) placed subcutaneously in the back of the animal, at a daily dose of 15 or 30 mg/kg body weight.

Data on graft survival in the various groups investigated are presented in Table 1. Controls rejected their allograft after a median survival time of 6 days, which was same for the group receiving cyclosporine alone at a daily dose of 1.5 mg/kg. Sinomenine at a daily dose of 15 or 30 mg/kg was as ineffective (median survival 5.5 and 6.5 days, respectively) as the combination of sinomenine at 15 mg/kg and cyclosporine at 1.5 mg/kg (median survival 7 days). In all cases graft histology showed cellular rejection, mostly scored as moderate. No obvious side effects were observed, as assessed by body weight, weight of major organs, and blood hematology (data not illustrated).

The results obtained do not confirm the claim by Candinas et al. [1], who used a similar stringent rat strain combination (donor RT1^a haplotype, recipient RT1^l haplotype). A major difference between the two studies, accounting for the divergence in results, is the dose and route of administration of cyclosporine. Candinas et al. [1] administered cyclosporine by daily intramuscular injection of 1.5 mg/kg, resulting in a marginal effect on graft survival (median survival 8 days). In contrast, we applied cyclosporine orally at 1.5 mg/kg per day, a dose that is not effective in the model. Since oral administration of cyclosporine leads to a lower exposure

Table 1 Heart allograft survival. Data shown are survival times for individual animals in each treatment group

Sinomenine (mg/kg per day)	Cyclosporine (mg/kg per day)	Survival	
		Days	Median (days)
Controls		5, 6, 6, 6	6
	1.5	5, 6, 6, 10	6
15		5, 5, 6, 6	5.5
30		6, 6, 7, 7	6.5
15	1.5	6, 7, 7, 8	7

than intramuscular administration, it seems likely that recipients in the study by Candinas et al. [1] had higher drug levels than the recipients in our study. Despite this lower exposure, animals subjected to daily oral administration of cyclosporine at 1.0–2.0 mg/kg are sufficiently exposed to reach long-term survival in synergy with suboptimal doses of the immunosuppressant SDZ RAD. We therefore conclude that sinomenine shows insufficient immunosuppressive activity or synergy with cyclosporine in rat heart transplantation in comparison with that of SDZ RAD. Our findings do not warrant further studies on this compound as a potential immunosuppressant in clinical transplantation.

References

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