The effect of methylprednisolone, naloxone, and spinal cord trauma on four liver enzymes: observations from NASCIS 2

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In order to determine the impact of extremely large doses of methylprednisolone, naloxone, or of spinal cord injury itself, on liver enzymes, we examined the results of SGOT, SGPT, alkaline phosphatase and total bilirubin tests obtained 24 hours, 3 and 10 days after the end of the study drug infusions in spinal cord injured patients entered in the National Acute Spinal Cord Injury Study.¹ The mean values of four liver enzymes, the amount of change between 24 hours and 3 and 10 days post infusion, and the proportion of liver enzyme levels considered to be abnormal did not appear to be affected by either drug protocol. Even when controlling for drug protocol and severity of injury (complete vs incomplete), variation in enzyme levels appeared to be the result of the spinal cord injury, not study drugs. Spinal cord injury is routinely treated with the NASCIS dose of methylprednisolone in many countries. It is reassuring to find no evidence of compromised liver function from this steroid protocol.

Keywords: spinal cord trauma; methylprednisolone; naloxone; liver enzymes; NASCIS 2.

Introduction

In a recently completed randomized clinical trial, the second National Acute Spinal Cord Injury Study (NASCIS2), methylprednisolone sodium succinate (MPSS) or naloxone hydrochloride (NAL) were compared to placebo to determine which showed greater efficacy in the return of neurological function after acute spinal cord injury.^{1,2} In this study 487 patients were randomized into one of three drug treatment protocols: those in the MPSS arm received a 30 mg/kg bolus for 15 minutes, followed 45 minutes later by a 5.4 mg/kg/h infusion of MPSS for the next 23 hours. Those receiving NAL were given a bolus of 5.4 mg/kg for 15 minutes, and 45 minutes later an infusion of 4.0 mg/kg/h of NAL for 23 hours. Those randomized to placebo were administered a placebo bolus and 23 hour placebo infusions for both drugs.¹

Because little is known about the effect of these drugs on liver cells at the doses used in this study, liver function tests (LFTs) were incorporated into the protocol to detect any adverse drug effects. These data were

closely monitored during the study. A search of the literature yielded one small study on the liver enzymes of 18 spinal cord injured patients.³ In this study, 76% or 13 of 17 patients had elevated SGPT values and eight of the 17 had elevated SGOT levels. Alkaline phosphatase levels were elevated in 10 out of 18 patients and bilirubin in three patients. No studies have been found assessing whether methylprednisolone or naloxone might have a deleterious effect on liver enzymes.

This paper addresses the following questions for four liver enzymes: (1) Do either MPSS or NAL compared to placebo bring about significant changes in liver enzymes? (2) Is there any impact on the liver from the spinal cord injury itself?

Methods

Liver function tests at 24 hours, 3 days, and 10 days after the end of the study drug infusion were required in the NASCIS2 protocol for all 487 randomized patients.

Nonetheless, 4–27% of patients were missing test results at one or more of these time intervals. Missing results, however, appeared to fall randomly across drug treatment, time of follow up, and need for surgery. Pretreatment LFTs were not requested for study patients because of the need to administer study drug as soon as possible.

We examined the values for four liver enzymes; SGOT, SGPT, alkaline phosphatase (ALKP), and total bilirubin. The mean values of these enzymes were calculated within each drug protocol at 24 hours, 3 days and 10 days after the end of study drug infusion. Analysis of covariance with placebo arm as the referent group was used to identify drug effects within these same three test periods, and also to control for severity of injury and drug protocol.

Within each drug protocol, enzyme values at 24 hours were subtracted from those at 3 and also at 10 days. *T*-tests were performed to determine whether the changes from the 24 hour levels were significantly different from the baseline 24 hour values. In order to detect any drug effects across drug protocols these mean changes were also examined by analysis of covariance, with placebo as the referent group.

Since not all study centers in this multicenter trial had the same predefined range for normal LFT values, an algorithm was developed for each center to determine the appropriate abnormal values for each of the four enzymes. The proportion of abnormal values in the three drug protocols was calculated for each test period. Chi square tests for trend were done to determine whether there were significant trends in the proportion of abnormal LFT values for the four enzymes between 24 hours and 10 days after the end of the drug infusion. All analyses were performed using the Statistical Analysis System (SAS).⁴

Results

SGOT

The mean SGOT values for patients in all protocols were highest 24 hours after infusion but declined by 3 days in all three protocols (Table I). No drug effect on

SGOT levels was found at 24 hours, but at 3 days SGOT levels in the NAL protocol were significantly lower than in the placebo group, with the MPSS group showing a borderline difference. By 10 days after infusion, the MPSS group had significantly lower SGOT levels compared to those of placebo patients. There was no difference between SGOT levels in NAL group and placebo group at 10 days.

When controlling for severity of injury (complete vs incomplete) and protocol in analysis of covariance, mean SGOT levels for patients with complete injury were significantly higher in all three test periods, compared to those who were incomplete. The highest mean SGOT values, according to severity of injury, were 91.8 u/l vs 63.8 u/l, $p = 0.0001$, which were recorded 24 hours after the end of infusion.

Next we subtracted the SGOT values at three and at 10 days post infusion from those at 24 hours to examine the magnitude of the change within these two test periods (Table II). We found a significant reduction in SGOT within each drug treatment by 3 days, and in MPSS and NAL by 10 days; the largest decrease in mean SGOT values being found in these two treatment arms at 10 days post infusion. However, in the analysis of covariance, where these changes were compared to those in the placebo group, the SGOT changes in MPSS and NAL groups were not significantly different from those of the placebo group, at either 3 or 10 days (Table II).

In analysis of covariance, controlling for severity of injury and protocol, the only outstanding change between the 24 hour time period and subsequent time periods occurred at 3 days after infusion. Complete patients had a significantly larger decrease in their SGOT levels compared to incomplete patients between 24 hours and 3 days, (-21.9 vs -7.2 , $p = 0.005$), but by 10 days post infusion the decrease in SGOT levels between complete and incomplete was similar (-12.6 vs -12.3 , $p = 0.98$).

The highest proportion of abnormal SGOT values was observed at 24 hours after the end of infusion, within all three drug treatments. A significant increase in normal SGOT values was observed for placebo and

Table I Mean values for liver function tests given 24 hours, 3 and 10 days after acute spinal cord injury in National Acute Spinal Cord Injury Study 2

Study group	Test time					
	24 hour	No.	3 days	No.	10 days	No.
<i>SGOT</i>						
MPSS	75.2	141	62.3	138	56.8	125
se	6.0		4.3		6.2	
p value	0.159		0.056		0.033	
Naloxone	79.9	134	59.9	129	66.3	125
se	6.1		4.4		6.2	
p value	0.40		0.024		0.301	
Placebo	87.1	146	73.9	138	75.2	134
se	5.9		4.3		6.0	
	R		R		R	
<i>SGPT</i>						
MPSS	44.4	135	58.6	135	94.3	119
se	4.0		3.9		10.0	
p value	0.23		0.763		0.143	
Naloxone	45.6	131	50.0	128	96.2	120
se	4.0		4.0		9.9	
p value	0.331		0.216		0.183	
Placebo	51.0	144	56.9	136	114.5	130
se	3.9		3.9		9.5	
	R		R		R	
<i>Alkaline phosphatase</i>						
MPSS	60.8	138	64.3	135	124.0	122
se	3.9		4.4		11.0	
p value	0.022		0.001		0.010	
Naloxone	69.0	133	75.9	124	151.1	122
se	4.0		4.6		11.0	
p value	0.423		0.179		0.424	
Placebo	73.4	146	84.4	141	163.2	134
se	3.8		4.3		10.4	
p	R		R		R	
<i>Total bilirubin</i>						
MPSS	0.27	143	0.33	136	0.30	121
se	0.03		0.03		0.04	
p value	0.963		0.41		0.129	
Naloxone	0.25	133	0.24	128	0.18	123
se	0.03		0.04		0.04	
p value	0.547		0.39		0.467	
Placebo	0.28	148	0.29	141	0.22	131
se	0.03		0.03		0.04	
	R		R		R	

R = Referent group; p value compares patients treated with MPSS or NAL to Placebo in analysis of covariance.

to a lesser extent for NAL patients at 10 days. The increase in normal values was not as large for MPSS treated patients (Table III).

When we controlled for severity of injury

and protocol, complete MPSS patients did not have a significantly higher proportion of abnormal values compared to those with incomplete injuries in any test period. NAL patients who were complete had

Table II Change in liver function levels from 24 hours and 3 days, and 24 hours and 10 days after completion of study drug infusion

Study drug	No.	Mean difference 3 days	<i>p</i> value ^a	No.	Mean difference 10 days	<i>p</i> value ^a
<i>SGOT(u/l)</i>						
MPSS	131	–12.55	0.009	117	–16.21	0.0025
se		4.35			8.3	
<i>p</i> value ^b		0.852			0.356	
Naloxone	124	–22.2	0.0001	124	–15.67	0.0194
se		4.47			8.19	
<i>p</i> value		0.173			0.378	
Placebo	130	–13.71	0.002	124	–5.56	0.616
se		4.37			8.02	
<i>SGPT (u/l)</i>						
MPSS	124	13.90	0.002	108	45.12	0.0001
se		3.43			10.5	
<i>p</i> value ^b		0.073			0.231	
Naloxone	120	3.52	0.32	120	53.15	0.0001
se		3.5			10.34	
<i>p</i> value		0.727			0.516	
Placebo	126	5.22	0.10	120	62.50	0.0001
se		3.4			10.0	
		R			R	
<i>Alkaline phosphatase (u/l)</i>						
MPSS	128	5.28	0.005	113	65.16	0.0001
se		2.71			10.6	
<i>p</i> value ^b		0.084			0.113	
Naloxone	119	8.05	0.0001	119	82.24	0.0001
se		2.81			10.45	
<i>p</i> value		0.325			0.67	
Placebo	131	11.88	0.002	124	88.43	0.0001
se		2.68			10.1	
		R			R	
<i>Total bilirubin (mg/dl)</i>						
MPSS	131	0.05	0.12	115	0.007	0.89
se		0.03			0.04	
<i>p</i> value ^b		0.24			0.17	
Naloxone	122	0.008	0.78	122	–0.07	0.016
se		0.03			0.04	
<i>p</i> value		0.89			0.98	
Placebo	131	0.002	0.91	120	–0.07	0.04
se		0.03			0.04	
		R			R	

R = Referent group.

^a*p* value comparing mean difference between 24 h and 3 days, and 24 h and 10 days in Student's *t*-test.^b*p* value comparing patients treated with MPSS, or NAL in placebo in analysis of covariance.

significantly higher proportions of abnormal SGOT levels at 24 hours and 3 days, and complete placebo patients had more abnormal levels at 24 hours and 10 days post infusion (Table IV).

SGPT

The mean values for SGPT are shown in Table I. Test values were increasingly elevated at 3 and especially at 10 days post infusion for those receiving placebo. There

Table III Proportion of normal and abnormal SGOT, SGPT, alkaline phosphatase, and total bilirubin levels in NASCIS 2 patients, by protocol

Time of test	Methylprednisolone			Naloxone			Placebo		
	Normal	Abnormal	No.	Normal	Abnormal	No.	Normal	Abnormal	No.
<i>SGOT levels</i>	(%)	(%)		(%)	(%)		(%)	(%)	
24 hours	26.2	73.8	141	19.4	80.6	134	25.3	74.7	146
3 days	33.3	66.7	138	31.0	69.0	129	23.9	76.1	138
10 days	34.4	65.6	125	31.2	68.8	125	40.3	59.7	134
	$\chi^2_2 = 2.11 \quad p = 0.146$			$\chi^2_2 = 4.65 \quad p = 0.031$			$\chi^2_2 = 7.23 \quad p = 0.007$		
<i>SGPT levels</i>									
24 hours	51.8	48.1	135	52.7	47.3	131	56.2	43.7	144
3 days	38.5	61.5	135	44.4	51.6	128	41.9	58.1	136
10 days	22.7	77.3	119	26.7	73.3	120	22.3	77.7	130
	$\chi^2_2 = 22.65 \quad p = \leq 0.0001$			$\chi^2_2 = 17.20 \quad p = \leq 0.0001$			$\chi^2_2 = 32.38 \quad p < 0.0001$		
<i>Alkaline phosphatase levels</i>									
24 hours	87.0	13.0	138	85.7	14.3	133	84.3	15.7	146
3 days	85.9	14.1	135	88.7	11.3	124	84.4	15.6	141
10 days	63.1	36.9	122	48.4	51.6	122	47.0	53.0	134
	$\chi^2_2 = 21.5 \quad p < 0.0001$			$\chi^2_2 = 45.32 \quad p < 0.0001$			$\chi^2_2 = 47.04 \quad p < 0.0001$		
<i>Total bilirubin levels</i>									
24 hours	58.7	41.3	143	49.6	50.4	133	53.8	46.2	145
3 days	62.5	37.5	136	49.2	50.8	128	56.0	44.0	141
10 days	58.7	41.3	121	52.9	47.1	123	58.0	42.0	131
	$\chi^2_2 = 6.33 \quad p = 0.98$			$\chi^2_2 = 0.256 \quad p = 0.61$			$\chi^2_2 = 0.50 \quad p = 0.48$		

 χ^2 test for trends.

was no significant effect of NAL or MPSS, compared to placebo, on SGPT levels at any time period.

However, when controlling for protocol and severity of injury, those with complete injury had significantly higher SGPTs in all three test periods. Values ranged from a low of 53.8 u/l and 36.6 u/l at 24 hours, $p = 0.0002$, to a high at 10 days post

infusion of 114.7 u/l and 82.5 u/l, $p = 0.005$.

The mean change between the 24 hour and 3 day SGPT levels was significant 3 days after infusion only for MPSS patients whose SGPT levels increased the most between 24 hours and 3 days post infusion. However, by 10 days after infusion there were significant increases in mean SGPT levels within all three drug treatments (Table II). When

Table IV Proportion of abnormal LFTs, by protocol and severity of injury

(a) Methylprednisolone

Severity	24 h	No.	3 days	No.	10 days	No.
<i>SGOT</i>	(%)		(%)		(%)	
Complete	76.0	96	71.0	93	71.4	84
Incomplete	68.9	45	57.8	45	53.7	41
<i>p</i> value	0.41		0.13		0.07	
<i>SGPT</i>						
Complete	53.3	92	64.4	90	86.2	80
Incomplete	37.2	43	55.6	45	59.0	39
<i>p</i> value	0.10		0.35		0.002	
<i>Alkaline phosphatase</i>						
Complete	13.4	95	13.0	92	42.2	83
Incomplete	11.6	43	16.3	43	25.6	39
<i>p</i> value	1.00		0.61		0.11	
<i>Total bilirubin</i>						
Complete	42.3	97	35.9	92	41.5	82
Incomplete	39.1	46	45.9	44	41.0	39
<i>p</i> value	0.86		0.58		1.00	

(b) Naloxone

<i>SGOT</i>						
Complete	90.5	74	77.5	71	73.5	68
Incomplete	68.3	60	56.6	58	63.3	57
<i>p</i> value	0.0002		0.02		0.25	
<i>SGPT</i>						
Complete	57.7	71	60.0	70	87.5	64
Incomplete	35.0	60	41.4	58	57.1	56
<i>p</i> value	0.014		0.05		0.0002	
<i>Alkaline phosphatase</i>						
Complete	15.1	73	10.4	67	61.2	67
Incomplete	13.3	60	12.3	57	40.0	55
<i>p</i> value	0.81		0.78		0.029	
<i>Total bilirubin</i>						
Complete	51.4	72	50.0	70	44.8	67
Incomplete	49.2	61	51.7	50	50.0	56
<i>p</i> value	0.86		0.86		0.59	

Table IV (Cont)

(c) Placebo

<i>SGOT</i>						
Complete	81.2	85	80.5	82	67.9	78
Incomplete	65.6	61	69.6	56	48.2	56
<i>p</i> value	0.036		0.159		0.032	
<i>SGPT</i>						
Complete	54.1	85	66.2	80	85.3	75
Incomplete	28.8	59	46.4	56	67.3	55
<i>p</i> value	0.003		0.023		0.019	
<i>Alkaline phosphatase</i>						
Complete	16.5	85	16.5	85	63.3	79
Incomplete	14.7	61	14.3	56	38.2	55
<i>p</i> value	0.822		0.815		0.005	
<i>Total bilirubin</i>						
Complete	51.2	84	49.4	85	40.3	77
Incomplete	39.3	61	35.7	56	44.4	54
<i>p</i> value	0.179		0.121		0.720	

these changes were compared across drug treatments, neither MPSS or NAL levels differed from placebo at 3 or 10 days (Table II).

When controlling for severity of injury and protocol, there was no difference in the change in SGPT levels of complete vs incomplete patients at either 3 (4.8 vs 11.7, $p = 0.09$) or 10 days post infusion (61.0 vs 42.6, $p = 0.13$).

In Table III the proportion of abnormal SGPT results is presented for the three drug treatments. By the 10th day after the end of drug infusion, significantly increased abnormal SGPT levels were observed within all three drug treatment groups.

When we controlled for severity of injury and protocol, there was a significantly higher proportion of abnormal SGPT levels in complete NAL and placebo patients in all three time periods, but only at 10 days for complete MPSS patients (Table IV).

Alkaline phosphatase

ALKP levels were elevated within all three treatment protocols 10 days after the end of infusion, especially for those receiving placebo (Table I). When ALKP levels were examined in each of the three treatments, they were significantly lower in the MPSS treated patients compared to placebo

treated patients at 24 hours, 3 and 10 days after infusion (Table I).

When controlling for severity of injury and protocol, mean values of ALKP were significantly higher for complete patients only at 10 days post infusion (164.8 vs 117.4, $p = 0.0002$).

The mean change at 3 and 10 days in ALKP levels was significant within all three drug treatments with the largest increases occurring in placebo and NAL treated patients (Table II). When we compared these changes across drug treatments, no significant differences between MPSS, NAL and placebo were found at 3 and 10 days (Table II).

When controlling for severity of injury and protocol, the increase in ALKP levels was significantly higher for patients with complete injury at 10 days after infusion only (100.7 vs 43.5, $p = 0.0001$).

A large proportion of ALKP levels remained normal up to 3 days after the end of the infusion in all three treatment arms, but by 10 days after infusion the proportion of abnormal levels had increased significantly in all three treatments with the highest proportions for NAL and placebo patients (Table III).

There was no significant increase in abnormal ALKP levels in complete vs incomplete patients randomized to MPSS in

any time period, but at 10 days post infusion, complete NAL and placebo patients had a significantly greater proportion of abnormal ALKP levels than those with an incomplete injury (Table IV).

Total bilirubin

There were no significant drug effects on total bilirubin levels across the treatment groups at any of the three test times (Table I). When controlling for severity of injury and for protocol there were no differences in total bilirubin levels for complete vs incomplete at any test period.

The change in mean total bilirubin levels 3 days after infusion was not significant within the three drug treatment groups, but by 10 days there were significant reductions in mean total bilirubin for NAL and placebo treated patients (Table II). When MPSS and NAL changes over this 10 day period were compared to placebo, there were no treatment effects that could be attributed to either drug (Table II).

When controlling for severity of injury and protocol, changes in bilirubin levels were similar at 3 (0.04 vs -0.014 , $p = 0.09$) and 10 days (-0.025 vs -0.069 , $p = 0.327$) for complete and incomplete patients.

There was also very little variation in the proportion of abnormal total bilirubin values over the 10 day period in the three treatment arms (Table III). When controlling for severity of injury and protocol, there were similar proportions of abnormal bilirubin values between complete and incomplete patients in all three drug protocols (Table IV).

Conclusions

We found no evidence that methylprednisolone or naloxone, compared to placebo, had any adverse effects on liver function.

To our knowledge, there are no published studies addressing possible drug-induced injury to the liver from either MPSS or NAL, particularly at the doses administered in NASCIS2, and only one study on abnormal liver enzymes after spinal cord injury.³ Many substances such as androgens,

steroids, antihypertensive drugs, or some antibiotics are known to cause hepatic dysfunction. The metabolism of drugs is also affected by many uncontrollable factors, including genetics, environment, and the rate of individual drug metabolism. The liver is able to adapt to drug exposure, by transforming some drugs which may be toxic in their lipid soluble state, into a less toxic, more water soluble form.

This study of possible drug effects on liver enzymes has been restricted for a number of reasons. Pretreatment LFTs were not part of the study protocol, so we have no baseline measurements of enzymes. The extent of alcohol use (or abuse) was also not available. Consequently, our data do not allow us to state with clinical certitude whether these observations on liver enzymes may be attributed to drug adaptation, drug injury, spinal cord injury, or some combination of these.

Because elevations in SGOT and SGPT are considered good measures of possible liver disease, we examined the mean levels in the three designated test intervals, the amount of change between the 24 hour test and 3 days, and 24 hours and 10 day, as well as the proportion of abnormal levels of these two enzymes.

While there were significant differences among the three treatment protocols in mean LFT levels, changes over test periods, and proportion of abnormal levels, the results for each LFT followed similar patterns regardless of study drug protocol. In all protocols the mean levels and the proportion of abnormal SGOT values peaked at 24 hours post infusion or about 2 days after injury, and declined thereafter. In contrast, Bloom & Freed reported peak SGOT levels at 35 days,³ but these cannot be compared with NASCIS2 data, where surveillance ended 10 days after the end of study drug infusion. Longer follow up in a large series of patients would be of interest.

The mean and highest proportion of abnormal SGPT and ALKP values were observed at 10 days post infusion in the three drug treatment groups. Bloom & Freed reported a peak of abnormal SGPT values at 29 days after injury. While they also reported elevated ALKP levels in 53%

of their patients, it is not clear how long after injury these increased levels peaked.³ The large differences between timing of peak liver enzyme levels in our study and those observed by Bloom & Freed are puzzling but may be due to the differences in study design and the size of the study population.

Although patients randomized to MPSS had the lowest mean levels and the lowest proportion of abnormal ALKP values at 10 days, the distribution of mean values and abnormal values followed a similar pattern across the three drug treatments.

Results of the total bilirubin tests did not add to our understanding of the effect of drug and injury. Bloom & Freed found only three out of 18 patients had abnormal total bilirubin levels.³

We examined SGOT and SGPT, ALKP and total bilirubin, controlling for severity of injury, and for protocol. Patients with complete spinal cord injury had higher mean SGOT and SGPT levels, higher proportions of abnormal values than those with an incomplete injury. Bloom & Freed reported that 10 out of 13 quadriplegics and three out of five paraplegics had elevated SGOT and SGPT levels³ which is in accord with our findings. Spinal cord patients with a complete injury often experience transient hypotension, and a loss of sympathetic tone, which will affect liver enzymes. Consequently, the more severe the injury, the more likely the patient will have increased perfusion of enzymes into the blood stream. Bloom & Freed's study³ and our data support our speculation that the magnitude of the injury is a primary contributor to elevated and abnormal LFT levels.

It is of interest that in our study SGOT and SGPT levels did not proceed in a similar direction, even when controlling for protocol and severity of injury. Because these divergent courses are independent of drug protocol, they may be due to an injury effect which is manifested differently through the two transaminases. This pattern was not observed by Bloom & Freed.³

MPSS appears to have a moderating effect on some enzymes. ALKP levels for MPSS patients were lower than those of placebo treated patients in all three test

periods. By 10 days post infusion, there was a higher proportion of normal ALKP levels in MPSS patients compared to NAL or placebo patients. When we controlled for severity of injury, MPSS complete and incomplete patients had similar proportions of abnormal ALKP, SGOT, and SGPT levels, except for SGPT at 10 days when complete patients had a significantly higher proportion of abnormal values. This suggests that MPSS may inhibit increasing levels of ALKP and SGOT, and to some extent SGPT, in spinal cord injured patients.

Measurements of mean and abnormal total bilirubin levels did not reflect any clear injury or drug response, whether or not we controlled for severity of injury.

We also examined the effects of surgery on liver enzyme levels of all patients who had spinal surgery. Three time periods were studied: from time to admission to 24 hours after infusion, from 24 hours up to 3 days after infusion, and from 3 to 10 days after infusion. We choose not to present these data because they were so similar to data presented for LFT analyses, irrespective of surgery. In addition, when the effects of surgery on liver enzyme levels were examined within these three test frames, the numbers of patients available for analyses were considerably reduced.

Mechanisms for increase in SGOT, SGPT and ALKP levels which appear to be injury related need to be investigated further. In future studies baseline LFTs would be informative as well as LFTs done later than 10 days after injury, to determine if or when liver function enzymes return to normal. Bloom & Freed found all LFT values returned to normal on an average of 42 days after injury.³ Since drug induced liver disease may be clinically inapparent, or may appear only transiently, testing at a later time, such as 1 month after injury, may provide some answers to these questions.

Since NASCIS2 patients received some of the largest doses of MPSS and NAL ever administered to any patient over 24 hours, it is of interest to note that no adverse drug effects were observed in the four liver enzymes tested in these patients.

MPSS has become part of standard

treatment for spinal cord injury, provided it can be administered within 8 hours of injury. It is reassuring that patients' liver function appears not to be compromised by this steroid protocol.

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References

- 1 Bracken MB, Shepard MJ, Collins WF *et al* (1990) A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. Results of the second National Acute Spinal Cord Injury Study, 1990. *N Engl J Med* **322**: 1405–1411.
- 2 Bracken MB, Shepard MJ, Collins WF *et al* (1992) Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study, 1992. *J Neurosurg* **76**: 23–31.
- 3 Bloom KK, Freed MM (1989) Liver enzyme abnormalities in spinal cord injury. *J Am Paraplegia Soc* **12**: 11–13.
- 4 Statistical Analysis System Institute (1982) *Supplemental Users Guide*. SAS Institute, Cary, NC.