Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial

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Summary

Background **Traumatic brain injury is a major cause of death and disability. We sought to assess the safety and efficacy of dexanabinol, a synthetic cannabinoid analogue devoid of psychotropic activity, in severe traumatic brain injury.**

Methods **861 patients with severe traumatic brain injury admitted to 86 specialist centres from 15 countries were included in a multi-centre, placebo-controlled, phase III trial. Patients were randomised to receive a single intravenous 150 mg dose of dexanabinol or placebo within 6 h of injury. The primary outcome was the extended Glasgow outcome scale assessed at 6 months, with the point of dichotomisation into unfavourable versus favourable outcome differentiated by baseline prognostic risk. Prespecified subgroup analyses were defined by injury severity, recruitment rate, and time to dosing. Secondary analysis included control of intracranial pressure and quality of life. Analysis were prespecified in the protocol and the statistical analysis plan. This study is registered with ClinicalTrials.gov, number NCT00129857.**

Findings **846 patients were included in the efficacy analysis. The extended Glasgow outcome scale at 6 months did not differ between groups; 215 (50%) patients in the dexanabinol group and 214 (51%) patients in the placebo group had an unfavourable outcome (odds ratio for a favourable response 1·04; 95% CI 0·79–1·36). Improvements in the control of intracranial pressure or quality of life were not recorded and subgroup analysis showed no indication of differential treatment effects. Dexanabinol was not associated with hepatic, renal, or cardiac toxic effects.**

Interpretation **Dexanabinol is safe, but is not efficacious in the treatment of traumatic brain injury.**

Introduction

Traumatic brain injury is a major cause of death and disability and is associated with high socioeconomic costs.[1–3] The primary injury initiates a complex sequence of events resulting in secondary brain damage, which can be exacerbated by systemic insults, such as hypoxia or hypotension. Therapeutic approaches focus on reducing secondary brain damage. Various neuroprotective drugs, mainly targeting specific pathophysiological mechanisms, have been developed and tested in traumatic brain injury, but convincing benefit of these drugs has not been shown.[4]

Dexanabinol is a synthetic cannabinoid analogue devoid of psychotropic activity, with strong neuroprotective potential. The drug differs from other neuroprotective drugs because it targets various pathophysiological mechanisms, including glutamate excitotoxicity,[5] free-radical damage,[6] and inflammatory response.[7–9] Dexanabinol was shown to be highly neuroprotective in an animal model of traumatic brain injury.[9]

Results from a phase I trial showed that dexanabinol was safe in healthy volunteers at doses up to 200 mg.[10] Results from a phase II study indicated improved control of intracranial pressure.[11] These findings, in combination with the good safety profile, instigated a phase III efficacy trial. The aim of this trial was to assess the efficacy and safety of a single intravenous dose of dexanabinol in severe traumatic brain injury.

Methods

Patients

This trial was started in Europe and Israel in January, 2001, was extended to Australia in 2002, and to the USA in 2003. 100 sites participated from 15 countries. The trial aimed to recruit 860 patients with severe traumatic brain injury. Enrolment criteria were specified to reduce heterogeneity of the population (panel).[12] Screening logs were obtained in collaboration with the European Brain Injury Consortium to monitor patient selection.

Local ethics committees and institutional review boards approved the trial for each centre. Because the population consisted of unresponsive patients, informed consent could not be obtained directly from the patients. Proxy consent was accepted at all centres. Deferred consent was allowed in some countries (Australia, Austria, Finland, France, and Germany) and in other countries (Israel, Italy, Spain, and the UK) consent for participation by an independent physician was allowed. In all cases in which a form of deferred consent was used, subsequent written confirmation by patient or proxy was obtained.

Procedures

Randomisation was undertaken according to a block design (block size=6) per centre in a 1:1 ratio of dexanabinol to placebo. The randomisation schedule was computer generated by the independent trial statistician. A double-blind trial design was used. Dexanabinol and placebo were supplied as identical looking solutions in identical glass vials. All trial personnel were unaware of treatment allocation during the entire trial period. Unblinding of the data occurred after hard lock of the clean database on Dec 6, 2004. An independent data safety monitoring board, unaware of treatment allocation, reviewed the trial results on an ongoing basis.

Patients were randomly assigned a single intravenous injection of 150 mg dexanabinol or placebo, given within 6 h of injury. Because dexanabinol is very lipophilic with low water solubility, the compound is dissolved in a cosolvent mixture that contains ethanol and Cremophor and is further diluted in 0·9% sodium chloride. The placebo vials contained the same cosolvent mixture. Before trial drug administration, antihistamine drugs (25 mg promethazine and 50 mg ranitidine) were given intravenously to reduce the risk of severe allergic reactions that could sporadically occur with the use of Cremophor.[13,14] The trial drug was given by infusion over 15 min. Follow-up CT scans were scheduled 18–48 h after the drug was given. Central CT readings, including classification according to the Traumatic Coma Databank,[12] were used for analysis. Hourly measurements of blood pressure, intracranial pressure, and therapy intensity level,[15] which indicated the intensity of intracranial pressure directed therapy, were recorded during the first 72 h. Laboratory investigations were scheduled before enrolment, on day 2, and on day 6, and ECG recordings were done before enrolment and on day 2. The patients' neurological status was carefully monitored for the occurrence of neuroworsening.[16]

All patients received the full range of standard treatment for the management of severe head injury as outlined in international guidelines.[17,18] Particular emphasis was placed on the prevention and treatment of secondary insults, the avoidance of intracranial hypertension, and maintenance of adequate cerebral perfusion pressure (>60 mm Hg). Concomitant treatments and medication were recorded.

Outcome was assessed during a personal interview at 3 months and 6 months according to the extended Glasgow outcome scale. A structured interview[19] was used to promote consistency in scoring. This standard assessment focused on consciousness, independence at home, independence outside home, work, social, and leisure activities, family and friendships, and return to normal life. The domain with the greatest level of dependence or disability determined the overall outcome score. Outcome assignments were centrally reviewed and discrepancies resolved after feedback to sites. The final investigator score was used for analysis. The Barthel index[20] and measures of quality of life (SF36[21] and the community integration questionnaire[22]) were obtained at the 6-month assessment.

The primary outcome measure was the extended Glasgow outcome scale assessed at 6 months (150–210 days) after injury. The safety outcomes included laboratory tests, adverse events, 12-lead electrocardiograms, and vital parameters. Prespecified endpoints for secondary analysis were early and late mortality, neuroworsening, control of intracranial pressure and cerebral perfusion pressure (mean arterial blood pressure – intracranial pressure), and quality of life.

Statistical analysis

The sample size was initially based on a proportional odds model used to analyse the primary efficacy variable. On the assumption that equal numbers are achieved in the three grouped outcome categories, a total sample size of 860 patients would give 90% power to detect a treatment effect size corresponding to a common odds ratio of 1·5 at the 5% significance level. In a protocol amendment dated May 4, 2004, the planned primary analysis was changed from the proportional odds model to the sliding dichotomy analysis. This approach aims to reduce the effect of differences in initial prognostic risk

***Panel:* Enrolment criteria**

Inclusion criteria

Age 16–65 years (as per local or national regulations)
Sustained head injury within the past 6 h
Injury severity requires intracranial pressure monitoring
Glasgow coma motor score of 2–5 with no eye opening and at least one reactive pupil
CT scan showing intracranial abnormality consistent with trauma (CT class >2)[12]
Haemodynamically stable after resuscitation (systolic blood pressure >100 mm Hg)
Female patients should be of non-childbearing potential or must have a negative pregnancy test
Patient has an informed consent form signed by either next of kin or legally acceptable representative. Informed consent obtained according to national or local legislation

Exclusion criteria

Head injury due to a penetrating foreign object
Any spinal cord injury
Major extracranial injuries causing continuous bleeding likely to require transfusion of more than 5 blood units within the first 12 h after injury
Coma due to pure epidural haematoma with an initial Glasgow coma motor score of >12
Known or CT scan evidence of previous major cerebral damage
Any severe concomitant disease (eg, cancer, haematological, renal, hepatic, or coronary disease) or chronic disorder (eg, psychiatric disorder) that can be ascertained at the time of admission
Coma suspected to be primarily due to causes other than head injury (eg, drug overdose)
Receipt of an experimental drug within 4 weeks prior to current injury
Administration of study drug is not possible within 6 h of injury
Suspected inability to obtain complete 6 months follow-up

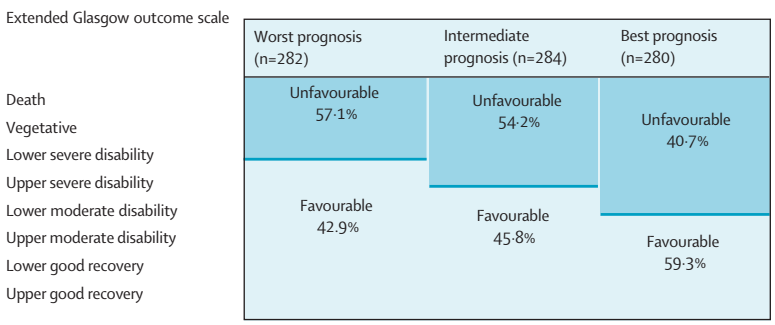

***Figure 1*: The sliding dichotomy**
Differentiation of the point of dichotomisation of the extended Glasgow outcome scale into unfavourable versus favourable outcome according to baseline prognostic risk.

on outcome analysis and has been advocated for use in trials of traumatic brain injury.[23] The sample size was not altered because we anticipated that this analysis would increase the statistical power of the trial.

For the primary efficacy analysis, according to the sliding dichotomy approach, dichotomisation of the 6-month extended Glasgow outcome scale for unfavourable versus favourable outcome was differentiated according to baseline prognostic risk. Briefly, for each patient a baseline prognostic risk score (BPRS) was calculated with seven predictors of outcome[24] obtained before randomisation—age, motor score, CT classification, pupillary reactivity, hypoxia and hypotension, and traumatic subarachnoid haemorrhage. Weighting of the BPRS factors was based on data from previous trials of traumatic brain injury. As the BPRS increases, so does the risk of poor outcome. The patient population was ordered on the basis of the BPRS and split into tertiles designated as worst prognosis, intermediate prognosis, and best prognosis. Within each tertile, the point of dichotomisation of the extended Glasgow outcome scale closest to a 50:50 split between better and worse outcome was identified (figure 1). The total proportion of patients from the three prognostic tertiles with a favourable outcome in the treatment group was compared with the corresponding proportion in the placebo group with a χ^2 test. The difference was quantified as an odds ratio with the corresponding 95% CI. As a further supporting analysis, the data were analysed with a proportional odds model,[25] which included age, motor score, CT classification, and pupillary reactivity as baseline covariates.

Data for intracranial pressure and cerebral perfusion pressure were summarised descriptively and differences between treatment groups were analysed with the Mann-Whitney test. The standard subscales of the SF36 and community integration questionnaire were used to assess quality of life and treatment groups were compared with the Mann-Whitney test.

Predefined subgroup analyses were by: recruitment rate (centres were ranked by monthly enrolment rate and grouped into tertiles); injury severity (CT classification and baseline motor score); and time to dosing (less than 4 h versus 4 h or more). As a further supporting analysis, all analyses were repeated for the per-protocol population, which excluded 107 patients (some meeting two or more exclusion criteria) because of serious violations of enrolment criteria (n=21), normal CT on central review (n=14), 6-month outcome data missing or outside window (n=38), and trial drug administration more than 6 h after injury (n=43). All analyses were conducted on an intention-to-treat basis; patients who did not receive the study drug (n=9) were excluded.

This study is registered with ClinicalTrials.gov, number NCT00129857.

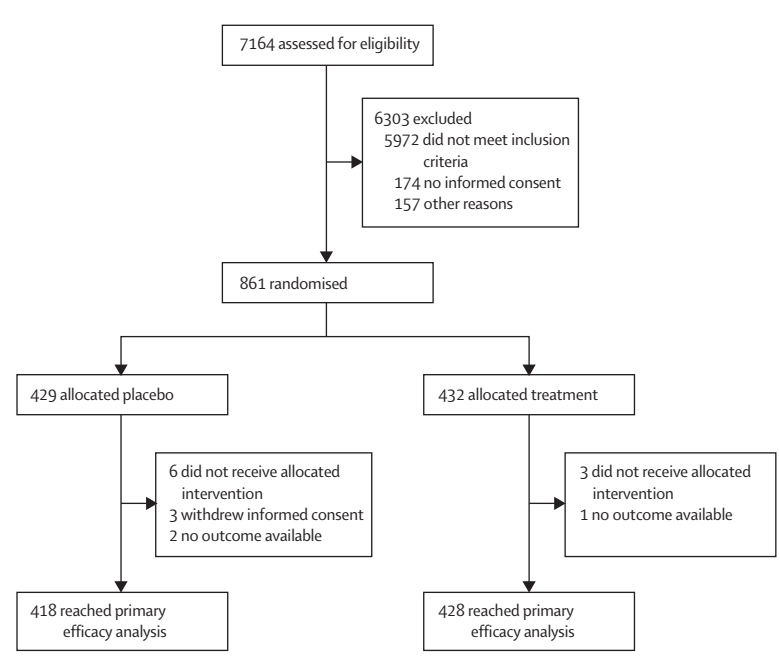

***Figure 2*:Trial profile**

Role of the funding source

The sponsor of the study provided study medication and financial support. The sponsor delegated full responsibility for scientific conduct of the study and data collection to the clinical members of the steering committee and to the contract research organisation Quintiles (Paris, France). The statistical analysis was done independently in collaboration between Quintiles and the trial statistician. No restrictions were imposed by the sponsoring company on the scientific conduct and interpretation of the trial. The corresponding author and the independent study statistician had full access to the original data, were provided with a full copy of the database, and had final responsibility for the decision to submit for publication.

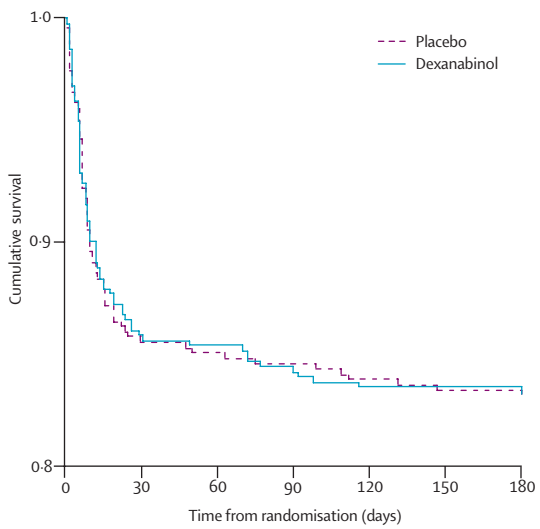

Figure 3: **Kaplan-Meier plot for survival**

Results

The trial was open to enrolment from Jan 1, 2001, to March 11, 2004. In total, 7164 patients were screened for participation, of whom 6303 were excluded: 5972 did not meet the enrolment criteria; informed consent could not be obtained (refusal or inability to contact relatives) for 174 patients; and 157 patients were not enrolled for other reasons, including unavailability of trial medication (13), temporary hold on recruitment (12), and patients missed for enrolment (112). For 20 patients the reason could not be determined because of incomplete data on the screening logs. A total of 861 patients were randomised at 86 sites in 15 countries (Australia, Europe, Israel, and the USA). 14 sites did not enrol any patients. The primary efficacy analysis included 846 patients (figure 2). Nine patients did not receive the study drug for the following reasons: deterioration to a condition that was irreversible (2); haemodynamic instability (2); improvement before dosing (1); history of anaphylaxis (1); normal CT scan (1); loss of study drug during preparation (1); and unknown reason (1). Baseline characteristics were well matched between the treatment groups (table 1).

There was no overall effect of dexanabinol on the 6-month extended Glasgow outcome scale assessment over the three prognostic bands (p=0·78; table 2). Consistent with the primary efficacy analysis according to the sliding dichotomy approach, secondary analysis with a proportional odds model showed no differences between treatment groups (1·07 [0·83–1·39]). There were no differences in mortality (figure 3), in the occurrence of neuroworsening, or in events related to recovery between the two treatment groups—ie, time to eye opening, time

	Placebo group (n=418)	Dexanabinol group (n=428)
Demographics		
Sex		
Men	345 (83%)	344 (80%)
Women	73 (17%)	84 (20%)
Cause of injury		
Road traffic accident	288 (69%)	308 (72%)
Falls	60 (14%)	55 (13%)
Other	70 (17%)	65 (15%)
Mean injury severity score (SD)	34·1 (12·2)	33·5 (12·3)
Baseline prognostic variables		
Mean BPRS score (SD)	2·95 (1·08)	2·92 (1·19)
Median age (IQR)	33 (23–46)	32 (22–45)
Qualifying GCS motor score		
1 no response	2 (<1%)	1 (<1%)
2 abnormal extension	42 (10%)	67 (16%)
3 abnormal flexion	99 (24%)	92 (21%)
4 flexion withdrawal	150 (36%)	121 (28%)
5 localising	125 (30%)	147 (34%)
Pupillary reactivity		
None reacting	12 (3%)	18 (4%)
One reacting	77 (18%)	72 (17%)
Both reacting	329 (79%)	338 (79%)
CT classification		
1 no abnormalities	8 (2%)	6 (1%)
2 diffuse injury	204 (49%)	205 (48%)
3 diffuse injury plus obliteration basal cisterns	89 (21%)	111 (26%)
4 shift, no mass lesion	25 (6%)	30 (7%)
5 any mass lesion (>25 mL)	89 (21%)	72 (17%)
Missing	3 (1%)	4 (1%)
Traumatic subarachnoid haemorrhage		
Present	257 (61%)	248 (58%)
Absent	161 (39%)	180 (42%)
Pre-enrolment hypoxia		
Present	101 (24%)	109 (25%)
Absent	317 (76%)	319 (75%)
Pre-enrolment hypotension		
Present	60 (14%)	67 (16%)
Absent	357 (85%)	361 (84%)
Unknown	1 (<1%)	0 (0%)

Data are number (%), unless otherwise stated.

Table 1: **Baseline characteristics of patient population**

	Placebo	Dexanabinol	Risk difference	Odds ratio* (95% CI)
Worst prognostic band (n=282)				
Unfavourable†	76	85	−3·1%	0·88 (0·55–1·41)
Favourable	61	60		
Intermediate prognostic band (n=284)				
Unfavourable‡	85	69	6·7%	1·31 (0·82–2·09)
Favourable	63	67		
Best prognostic band (n=280)				
Unfavourable§	53	61	−1·6%	0·93 (0·58–1·51)
Favourable	80	86		
All bands (n=846)‖				
Unfavourable	214 (51%)	215 (50%)	1·0%	1·04 (0·79–1·36) p=0·78
Favourable	204 (49%)	213 (50%)		

Worst prognostic band=BPRS>3·61; intermediate prognostic band=BPRS 2·3–3·61; best prognostic band=BPRS<2·38; †extended Glasgow outcome scale lower severe disability or worse; ‡extended Glasgow outcome scale upper severe disability or worse; §extended Glasgow outcome scale lower moderate disability or worse; ‖test for interaction χ^2=1·61, p=0·45; an odds ratio >1 indicates a beneficial effect of dexanabinol, an odds ratio <1 indicates an adverse effect.

Table 2: **Primary efficacy analysis**

	Placebo	Dexanabinol
Time to eye opening (days)		
Sample size	333	336
Mean (SD)	9·8 (8·5)	9·7 (6·4)
Median (IQR)	8 (3–14)	9 (5–14)
Time to obeying commands (days)		
Sample size	241	246
Mean (SD)	10·6 (10·2)	11·6 (9·6)
Median (IQR)	8 (4–15)	10 (5–16)
Duration of ventilation (days)		
Sample size	359	368
Mean (SD)	14·3 (11·1)	13·7 (9·4)
Median (IQR)	13 (6–20)	12 (7–18)
Neuroworsening		
Number of patients with any episode within the first 10 days	186 (44%)	189 (44%)

Table 3: **Recovery and deterioration**

	Placebo (n=410)	Dexanabinol (n=423)
Percentage time ICP>20 mmHg		
Mean (SD)	18·0 (26·1)	19·8 (25·8)
Median (IQR)	5·7 (0·0–23·7)	7·1 (1·5–28·6)
Percentage time ICP>25 mmHg		
Mean (SD)	9·7 (20·9)	10·4 (19·6)
Median (IQR)	1·4 (0·0–7·2)	1·6 (0·0–10·3)
Percentage time CPP<60 mmHg		
Mean (SD)	11·8 (17·9)	11·4 (16·8)
Median (IQR)	5·6 (1·4–14·3)	5·2 (1·4–14·9)
Percentage time CPP<50 mmHg		
Mean (SD)	4·2 (13·4)	3·9 (12·6)
Median (IQR)	0·0 (0·0–2·9)	0·0 (0·0–2·8)

ICP=intracranial pressure; CPP=cerebral perfusion pressure.

Table 4: **Control of intracranial pressure and cerebral perfusion pressure**

to obeying commands, and duration of ventilation (table 3). Furthermore, there were no beneficial effects of dexanabinol for improving control of intracranial pressure and cerebral perfusion pressure (table 4) or quality of life (table 5).

Prespecified subgroup analysis showed no significant differential treatment effect (figure 4). A trend towards possible benefit of dexanabinol was noted in the intermediate prognostic band (risk difference 6%) and in high-enrolling centres (risk difference 7%), but the differences were not significant (p=0·26 and 0·29, respectively). There was no evidence of heterogeneity for any of the four subgroup analyses. Analysis of the per-protocol population did not yield different results. The odds ratio for a favourable response to dexanabinol was 0·94 (95% CI 0·70–1·25) and none of the secondary comparisons showed significant results.

The observation of a trend towards efficacy in the high-enrolling centres prompted further exploratory analysis of the performance of centres related to case load (monthly enrolment rate). There were fewer exclusions for the per-protocol population (p<0·001) and the average number of adverse events reported per patient was higher (p<0·001) in the high-enrolling centres than in the low-enrolling and intermediate-enrolling centres (table 6). Furthermore, mortality was lower (p=0·05) and a trend was noted towards more favourable outcome (p=0·11) in the high-enrolling centres. Subgroup analysis by sex showed no differential treatment effect. The percentage of favourable outcome for women in the placebo group was 51% (37/73) and in the dexanabinol group was 46% (39/84). Although there were few women in the trial, there was clearly no evidence of sex-related differences in efficacy and, in particular, there was no suggestion of a beneficial effect of dexanabinol in women.

Adverse events were reported in 95% of patients in both groups. Possible treatment-related adverse events were reported in 25 patients in the dexanabinol group and in 32 patients in the placebo group. In one patient a clear cell carcinoma of the kidney was identified before randomisation on CT examination of the abdomen. Serious adverse events were reported in 39% of patients in the dexanabinol group and in 42% of patients in the placebo group (table 7).

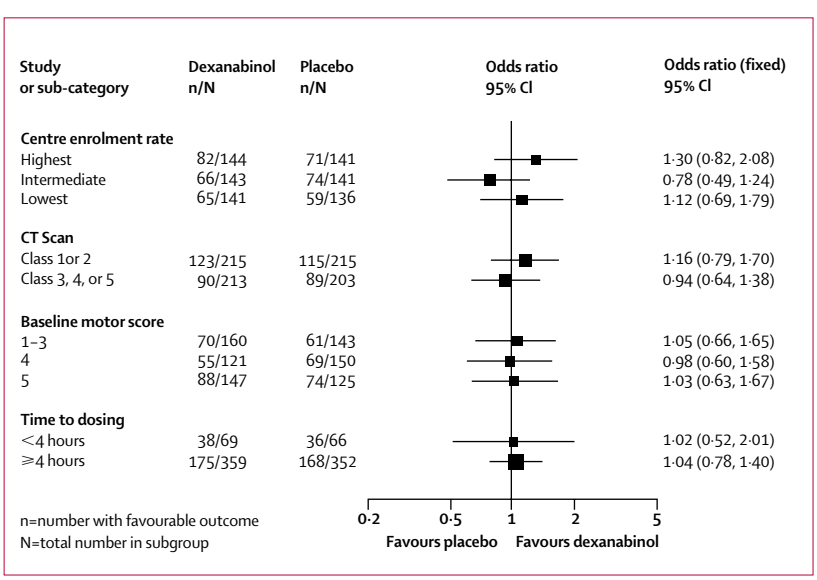

Figure 4: **Prespecified subgroup analysis**

	Placebo	Dexanabinol
CIQ*		
Sample size	277	297
Median (IQR)	14·3 (10–19)	13·3 (8·5–18)
SF36*		
Sample size	294	314
Median physical composite score (IQR)	43·6 (36·2–53·3)	43·2 (33·5–52·6)
Median mental composite score (IQR)	48·4 (35·9–55·9)	47·6 (35·0–56·2)
Barthel index		
Sample size	335	345
Mean (SD)	79 (36)	82 (32)

*Quality of life assessments done only in patients with an extended Glasgow outcome score>3 who were able to communicate adequately. CIQ=Community Integration Questionnaire

Table 5: **Quality of life and Barthel index**

Follow-up ECG did not show any differences between patients in the dexanabinol and placebo groups for the occurrence of arrhythmias, conduction abnormalities, or QT prolongation. Laboratory investigations showed many abnormal values, consistent with the multiple injuries many patients had sustained. No differences were observed in mean values between treatment groups at baseline or at follow-up.

	Low* (n=277)	Intermediate† (n=284)	High‡ (n=285)
Mortality rate at 6 months	19%	18%	12%
% unfavourable outcome	55%	51%	46%
Mean number of adverse events/patient	5·1	6·9	9·9
Exclusions per protocol population	17%	15%	6%

*<0·44 cases per month; †0·44–0·83 cases per month; ‡>0·83 cases per month

Table 6: **Case load and performance by enrolment rate**

Discussion

The results of this trial show the safety of dexanabinol in the treatment of traumatic brain injury, but do not show efficacy. Overall, there was an observed absolute increase in the proportion of patients with a favourable outcome of 1% in the dexanabinol group.

Previous studies in traumatic brain injury have not convincingly shown efficacy of various neuroprotective agents.[4] Some of these studies were initiated with an insufficient preclinical workup and with insufficient knowledge of appropriate dosing and brain penetration.[26] Although many drugs might have been truly ineffective, the lack of statistical significance of some interventions could have been due to a combination of over-optimistic expectations, underpowered studies, and insensitive methods.[4,27,28] As a consequence, further development of potentially effective neuroprotective drugs has been discontinued and the modest but clinically relevant treatment benefits are surrounded with uncertainty.

The decision to undertake a phase III trial with dexanabinol was based on the proven safety profile, evidence of efficacy in relevant animal models, and promising preliminary clinical data. The excellent safety profile was confirmed in patients with traumatic brain injury in the current trial. Experimental data have consistently shown better protection the sooner a neuroprotective drug is given after injury.[29,30] Experimental studies in a model of traumatic brain injury showed that dexanabinol given up to 3 h after trauma is protective against breakdown of the blood–brain barrier, reduces oedema formation, and decreases the number and severity of neurological signs.[9] When given 4–6 h after trauma, the compound still provides clear improvement of neurological symptoms, but no longer significantly reduces oedema. Consequently, the experimental time window for pathophysiological endpoints is 3 h, and for behavioural endpoints is 4–6 h. Whether these time windows can be extrapolated to the clinical situation is uncertain. In this study, 75% of patients received the trial drug later than 5 h after injury and greater protection might have been achieved with earlier administration. However, subgroup analysis of patients treated within 4 h after injury did not show any indication of benefit.

Selection of the single dose of 150 mg dexanabinol was based on pharmacokinetic studies in the experimental situation and in healthy volunteers. In rats a single intravenous dose of 5 mg/kg caused a peak plasma concentration in the range 4000–5000 ng/mL at which neuroprotection was shown. In healthy volunteers, a single intravenous injection of 150 mg consistently showed peak plasma concentrations in the range of 5000 ng/mL.[10] However, the distribution volume in patients with traumatic brain injury might differ from that in healthy volunteers. In traumatic brain injury, the combination of blood loss and the vasodilatory effects of sedative drugs mandates vigorous fluid administration. This concern was considered in the design of the trial, and patients in whom substantial blood transfusions were anticipated were excluded. Nevertheless, we noted a high fluid input in many patients. Almost 50% of patients received over 300 mL per h on day 1. Unfortunately, data for the effect of this liberal fluid administration on distribution volume and concentrations of dexanabinol are not available, but plasma concentrations could have been below therapeutic levels. Post-hoc subgroup analysis, however, did not show any treatment benefit in patients receiving less than 300 mL per h on day 1. 49% of these patients had a favourable outcome with dexanabinol, compared with 51% in the placebo group. We also recorded a significant association between hourly fluid input and BPRS (p=0·004), such that more fluids were given to high-risk patients. In retrospect, the absence of data on plasma concentration of dexanabinol in this trial can be considered a significant limitation of the study design.

We could not confirm the beneficial effect of dexanabinol shown in the phase II trial[11] for improvement of control of intracranial pressure and cerebral perfusion

	Placebo	Dexanabinol
Any serious adverse event	175	167
Blood and lymphatic system disorders	7	7
Cardiac disorders	5	11
Endocrine disorders	5	5
Gastrointestinal and hepatobiliary disorders	9	6
Deep venous thrombosis	2	1
Acute respiratory distress syndrome	8	10
Infection	42	36
Pneumonia	16	23
Sepsis	17	9
CNS disorders	104	101
Brain oedema	25	21
Severe intracranial pressure increase	55	56
Seizures	5	7

Data are number of patients with at least one report of the relevant adverse event.

Table 7: **Serious adverse events**

pressure. In that trial, undertaken in 67 patients with severe traumatic brain injury, the average proportion of time that intracranial pressure was more than 25 mm Hg was about 3% in the dexanabinol group and more than 12% in the placebo group. Data for intracranial pressure were, however, available for only 30 patients treated on day 1 and for only 12–15 patients on day 3. The effect reported in the phase II trial could have been due to the small sample size and differences in baseline characteristics. In the placebo group, the basal cisterns, a prominent predictor of intracranial hypertension,[31] were compressed in 47% of patients in the dexanabinol group compared with 54% of patients in the placebo group. Consequently, in retrospect, the generalisability of the phase II data should be questioned.

Potential difficulties due to the heterogeneity of the patient population and the lack of sensitivity of the outcome measure were both addressed by use of the sliding dichotomy approach[22] in the extended Glasgow outcome scale analysis.

Mortality rate at 6 months (17%) was lower than in previous trials of traumatic brain injury (20–27%).[32] This low rate is remarkable since the enrolment criteria targeted a more severely injured population than have previous trials. Whether this low mortality rate reflects improved standards of care or might have been a result of possible neuroprotective effects of the premedication (anti-histamine medication), which was administered to all patients, is unclear. Histamine has been identified as a mediator in the breakdown of the blood–brain barrier and in oedema formation.[33] The possibility of an interaction between the anti-histamine medication and the study drug, which could potentially decrease efficacy, was considered but deemed very unlikely, especially in relation to the beneficial finding in the phase II trial in which all patients also routinely received anti-histamine prophylaxis. Furthermore, experimental studies have shown no effect of anti-histamines on the pharmacokinetics of dexanabinol.

We noted a better performance and a trend towards better outcome in centres with a high case load than in those with a low case load. The difference in study performance indicates better study compliance and closer observation of patients in high-enrolling centres. Interpretation of the trend towards better outcome in high-enrolling centres should, however, be with caution, because a marginal imbalance in the BPRS (p=0·06) was recorded between groups with the lowest recruiters having the highest risk profile.

To our knowledge, this study was the first trial of a neuroprotective drug in traumatic brain injury to use the extended Glasgow outcome scale, an outcome measure of presumed increased sensitivity, and included innovative statistical approaches. We found that the prognostic model, underlying the sliding dichotomy, was effective, with the proportion of patients with moderate disability or good recovery (the traditional split for dichotomisation) in the poor, intermediate, and good prognosis bands being 32%, 46%, and 70%, respectively. The sliding dichotomy yielded more appropriate definitions of favourable outcome for each of the three bands (figure 1).

These data confirm that the new approaches undertaken in this trial are valid, but further work is needed to ascertain the benefits, and final confirmation can only be obtained after conclusion of a positive trial. The concept of neuroprotection in traumatic brain injury remains appealing, and the scientific challenge will be to maximise chances for showing benefit of new treatments.

Writing committee
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