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Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke.
Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD000211.
DOI: [10.1002/14651858.CD000211.pub2](https://doi.org/10.1002/14651858.CD000211.pub2).

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[Intervention Review]

Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke

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Editorial group: Cochrane Stroke Group

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Bath PMW. Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD000211. DOI: [10.1002/14651858.CD000211.pub2](https://doi.org/10.1002/14651858.CD000211.pub2).

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ABSTRACT

Background

Theophylline causes potent cerebral vasoconstriction which decreases blood flow in the non-ischaemic areas of the brain and increases collateral blood flow surrounding the ischaemic region. NOTE: This review covers an area where no active research is taking place. It will be updated if relevant information becomes available.

Objectives

To assess the effect of theophylline and its analogues, aminophylline and caffeine, in people with confirmed or presumed acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched November 2003). For the first version, we also searched EMBASE (1980 to 1999), MEDLINE (1966 to 1999) and Science Citation Index (1981 to 1999). We also contacted the principal investigators of the identified trials.

Selection criteria

Randomised trials of theophylline or an analogue compound compared with placebo or control in people with confirmed or presumed acute ischaemic stroke. Trials were included if treatment was started within one week of stroke onset.

Data collection and analysis

Three reviewer authors applied the inclusion criteria, assessed trial quality and extracted data for the first version. The review was updated by one review author.

Main results

Two trials involving just 119 patients were included; six studies were excluded. Trial quality was good. Both of the trials tested aminophylline. Analysis was by intention to treat where possible. No significant difference was shown in early case fatality (within four weeks) between aminophylline and placebo although the confidence intervals were wide (odds ratio (OR) 1.12, 95% confidence interval (CI) 0.49 to 2.56). There was no significant difference for early death and deterioration (OR 0.87, 95% CI 0.41 to 1.88). Death or disability was not significantly reduced by treatment based on 73 patients in one trial (OR 0.64, 95% CI 0.24 to 1.68). Data for late death and disability were not in a form suitable for analysis. No data on quality of life were available.

Authors' conclusions

There is not enough evidence to assess whether theophylline or its analogues, e.g. aminophylline, are safe and improve outcome in people with acute ischaemic stroke.

PLAIN LANGUAGE SUMMARY**Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke**

Theophylline and related drugs, which can enlarge brain blood vessels, are of no apparent benefit in the early treatment of strokes caused by blood clots. Most strokes are caused by a blood clot which then reduces blood flow in the affected part of the brain. Without an adequate blood supply, the brain quickly suffers damage which is often permanent. Drugs which can improve brain blood flow might reduce damage and improve outcome after stroke. Theophylline and related drugs have the ability to alter brain blood flow. This systematic review assesses whether this type of drug improves outcome after stroke. The review identified two small trials, neither of which found any benefit. The limited amount of data mean that there is no evidence at present to suggest that theophylline and related drugs should be used in acute stroke.

BACKGROUND

Stroke is the third most common cause of death in the Western world and the most common cause of long-term adult disability. However, limited treatment options exist: aspirin has a wide utility but small effect whilst the converse is true for alteplase.

Theophylline (di-methyl xanthine), aminophylline (theophylline-ethylenediamine, a conjugated preparation of theophylline used to increase solubility for intravenous administration) and caffeine (tri-methyl xanthine) are all methylxanthines with related chemical structures. Theophylline relaxes smooth muscle, has a positive inotropic effect ([Simaan 1976](#)), increases ventilation, dilates coronary vessels, promotes diuresis and produces central stimulation. It is mainly used for the treatment of asthma as it has bronchodilatory properties. Theophylline acts through several mechanisms including inhibiting cAMP phosphodiesterase, antagonising adenosine and altering intracellular calcium transport mechanisms. However, the relative importance of these effector pathways in mediating vasodilation and bronchodilation are currently undefined. The cerebral stimulant effect may also have some importance in acute stroke.

Theophylline causes potent cerebral vasoconstriction ([Gottstein 1972](#); [Regli 1971](#)). This occurs by an 'inverse intracerebral steal' effect ([Paulson 1974](#); [Skinhoj 1970](#)). The vasoconstriction decreases cerebral blood flow in the non-ischaemic areas and increases collateral blood flow surrounding the ischaemic region ([Magnussen 1977](#)). In embolised rats, theophylline reduced cerebral oedema and mortality ([Kogure 1975](#)). Theophylline is therefore a candidate treatment for acute ischaemic stroke.

There have been several uncontrolled open studies where intravenous theophylline or aminophylline were administered to stroke patients. These have reported improvements in neurological impairment ([Mainzer 1949](#); [Olivarius 1957](#); [Olivarius 1961](#); [Olivarius 1970](#); [Schlegel 1952](#); [Schmidt-Voigt 1951](#)). The doses given were similar to those used in the treatment of asthma and were carefully controlled as methylxanthines have a narrow therapeutic index.

A number of randomised controlled trials of theophylline or aminophylline in the treatment of acute ischaemic stroke have been undertaken. This Cochrane analysis presents a systematic review of these randomised controlled trials.

Note: the use of the words theophylline and aminophylline have been used interchangeably as aminophylline is a preparation of theophylline and essentially has the same pharmacological actions.

OBJECTIVES

To determine whether theophylline and its analogues are a safe treatment for patients with acute confirmed or presumed ischaemic stroke and whether they reduce early and late case fatality, combined case fatality and neurological deterioration, and combined case fatality and disability.

METHODS

Criteria for considering studies for this review

Types of studies

All truly randomised unconfounded controlled parallel group trials examining the effects of theophylline administered within one week of confirmed or presumed acute ischaemic stroke. Crossover trials, where all subjects receive active and control treatment in random order, were excluded.

Types of participants

Patients within one week of acute stroke who were not known to have had a primary intracerebral haemorrhage.

Types of interventions

Intravenous or oral theophylline (or analogue) versus placebo or nothing, or theophylline (or analogue) plus another drug versus that other drug. Protocols involving comparison of theophylline (or analogue) and another drug versus placebo or nothing were excluded.

Types of outcome measures

The primary outcome measure was early case-fatality (within one month); secondary outcome measures included: late case fatality (more than one month), death or neurological deterioration at scheduled end of follow-up, death or disability at scheduled end of follow-up, length of stay in hospital, quality of life, and side effects. Deterioration refers to a worsening in neurological condition, however determined by the trial authors, following randomisation.

Search methods for identification of studies

See: 'Specialized register' section in [Cochrane Stroke Group](#)

Relevant trials were identified in the Cochrane Stroke Group trials register, which was last searched by the Review Group Co-ordinator in November 2003.

For the first version of this review, we also searched EMBASE (1980 to 1999), MEDLINE (1966 to 1999) and Science Citation Index (1981 to 1999). Electronic search terms included: (stroke or cerebr*) and (theophylline or aminophylline or caffeine or caffeinol or methylxanthine or afonilum or aminophyllin or cardophyllin or clonofilin or duraphyllin or escophylline or etophyllin or eufilina or euphyllin* or inophylline or palaron or pecram or peterphyllin or phylocontin or phylotemp or planphylline or tefamin or xanthinol nicotinate or zepholin). The latter compounds are preparations of aminophylline or theophylline.

In an effort to identify published and unpublished trials we contacted the manufacturers of theophyllines in 1999: 3M Health Care Ltd, UK; Astra Pharmaceuticals, UK; Lipha Pharmaceuticals, UK; Napp Laboratories, UK; Pharmax, UK; and Zyma Healthcare, UK. Additional information was sought from the principal investigators of the identified trials, and reviews of xanthine derivatives in cerebrovascular disease.

Data collection and analysis

In earlier versions of this review, two review authors independently selected trials and extracted information from published reports; we also sought additional information from the principal

investigators of these trials. For this update, relevant trials and abstracts were screened by the present review author (PB).

We noted information on the method of concealment of allocation, blinding, analysis (intention-to-treat versus efficacy), the number of patients randomised, dose, route and timing of theophylline, patient withdrawals, case fatality, neurological deterioration, disability, length of stay in hospital, quality of life and side effects occurring in each trial.

We assessed the methodological quality of trials, as detailed in the Cochrane Handbook. We tested for heterogeneity and calculated a weighted estimate (fixed-effect model) of the typical treatment effect across trials (odds ratio), using the Peto method, with the Cochrane Review Manager software, RevMan 4.2.

Information on all patients originally randomised was sought, irrespective of whether or not they actually received their trial treatment, and whether or not they completed the trial follow-up procedures. Attempts were made to seek the vital status of all randomised patients at the time of final scheduled follow up. Patients without disability at follow up for whom only 'dead or alive at final follow up' was known were not excluded from the analysis.

RESULTS

Description of studies

See 'Characteristics of included studies' table. No ongoing trials have been identified and none are awaiting assessment. Six studies were excluded (see 'Characteristics of excluded studies' table).

Both of the trials used aminophylline for the treatment. For the placebo group one trial used physiological saline (Geismar 1976) and the other used 5.5% glucose (Britton 1980). Aminophylline was administered as either a 200 mg intravenous bolus dose (10 ml 2% solution in saline) infused over two minutes followed by 10 ml at three hours and 10 ml at six hours (Geismar 1976), or by intravenous loading dose of 230 mg followed by continuous intravenous infusion (0.5 mg/kg/h in 5.5% glucose) for 72 hours (Britton 1980).

One trial reported change in neurological impairment using a locally developed scoring system (Geismar 1976); this trial also reported the Rankin score at three weeks. The other trial reported changes in functional capacity, based on the patients ability to walk (Britton 1980). None of the trials reported quality of life.

Risk of bias in included studies

Two trials were identified which met our inclusion criteria and have been included in the analysis. The methods used in the trials are summarised in the 'Characteristics of included studies' table. The trials were double-blind (i.e. both patients and investigators were blinded to treatment), placebo-controlled, and truly randomised. One trial randomised patients by sealed numbered envelopes (Britton 1980); the other trial was randomised by coded numbered boxes (ampoules) supplied by the hospital pharmacist (Geismar 1976). None of the studies explicitly stated that they were analysed by intention-to-treat, however, it is clear in one trial (Britton 1980) that no patients were lost to follow up; six patients were lost to follow up in the trial of Geismar (Geismar 1976), three in the treatment group and three in the control group. Both trials were single centre and involved 79 (Geismar 1976) and 46

(Britton 1980) patients respectively. One trial used lumbar puncture CSF analysis in two-thirds of the patients to exclude cerebral haemorrhage (Geismar 1976), the other used lumbar puncture or brain scintigraphy (Britton 1980). Due to the unavailability of CT scanning at the time of these trials, some patients with primary intracerebral haemorrhage may have inadvertently been studied. Enrolment varied from within 96 hours (Geismar 1976) to within 114 hours (Britton 1980). In one of the trials (Britton 1980), an independent neurological assessor was used to minimise bias in outcome assessment.

Effects of interventions

The total number of subjects in the two analysed trials numbered 119 (excluding the six patients lost to follow up in the trial of Geismar, three from each of the treatment and control groups). The average age of patients in the trials was 74 years and almost half were male. There was no evidence of statistical heterogeneity in either analyses: early case fatality (chi sq 0.19, df = 1, $p > 0.10$), early case fatality or neurological deterioration (chi sq 0.01, df = 1, $p > 0.10$).

Treatment with aminophylline was associated with a non-significant 12% increase in the odds of early case fatality (95% confidence interval (CI) 51% reduction to 156% excess). Assessment of the combined outcome of early death or neurological deterioration showed a non-significant reduction in odds of 13% (95% CI, 59% reduction to 88% excess). Similarly, a non-significant reduction of 36% in the odds of death or disability was found in the Geismar trial (OR 0.64, 95% CI 0.24 to 1.68) (Geismar 1976). The effect of the six missing patients in the Geismar trial was assessed using a sensitivity analysis. In the worst case, the three patients in the treatment group could have died and the three in the control group could have lived; in this scenario the overall odds ratio for early case fatality increased from 1.12 to 1.42 and that for combined case fatality or deterioration increased from 0.87 to 1.09. In contrast, the three missing patients in the treatment group could have lived whilst those in the control group died; the odds ratios then fell to 0.86 and 0.71 respectively for case fatality, and combined case fatality or deterioration.

No side effects or serious adverse events were reported in either of the two trials. However, numerous side effects have been reported with the use of aminophylline with asthma. Aminophylline has a narrow therapeutic index so the doses investigated were those used in the treatment of asthma (range 55 to 110 umol/l).

DISCUSSION

This review summarises the two randomised controlled trials of theophylline or analogues in acute ischaemic stroke. The overall results do not support the hypothesis that theophylline or its analogues reduce early case fatality following stroke. However, the confidence intervals are wide reflecting the extremely low numbers of patients studied, and aminophylline could equally reduce the odds of short-term mortality by 51% or increase it by 156%. Analysis of the combined end point of early case-fatality or neurological deterioration found that the odds for this combined outcome was non-significantly reduced by 13%.

Aminophylline was administered between 18 to 114 hours (Britton 1980) and within 96 hours of stroke onset (Geismar 1976). Delayed administration, beyond perhaps six to 12 hours, is unlikely to be as

beneficial as early intervention since ischaemic damage is likely to have become permanent by this time.

The primary method of excluding primary intracerebral haemorrhage used CSF criteria in both trials; this raises the possibility that patients with haemorrhage were included which would be potentially detrimental since methyl-xanthines can inhibit platelet function.

No information was available for late death, length of stay or quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

Existing randomised controlled trials of theophylline or aminophylline do not provide any evidence of reduced case fatality following acute ischaemic stroke. However, the numbers of trials and participants studied are too small and trial designs were suboptimal so that further research may be required.

Theophylline or aminophylline should not currently be used in the routine management of acute ischaemic stroke.

Implications for research

The existing trials show no definite evidence that aminophylline causes harm or benefit when administered at doses suitable for the treatment of asthma; however, moderate hazard or benefit cannot be excluded. However, the numbers of patients studied was small and aminophylline was generally administered late (after 24 hours). Hence, one or more larger trials of theophylline or analogues may be warranted in acute ischaemic stroke; however, the unpromising nature of the limited evidence already available for theophylline suggests that resources should probably be concentrated on other more promising treatments.

If the original trial data are still available, particularly those relating to neurological impairment, disability, blood pressure and adverse events, it may be possible to further assess the effects of theophylline on morbidity.

ACKNOWLEDGEMENTS

Mr AA Mohiuddin and Dr FJ Bath contributed to and co-authored earlier versions of this review. We are grateful to the Editorial Board of the Cochrane Stroke Group and external peer reviewers for making constructive comments on this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Britton 1980

Methods	Randomisation by sealed numbered envelopes Double-blind placebo controlled Intention to treat No loss to FU Single centre trial.
Participants	Sweden 24 male, 22 female Mean age 75 years Enrolment within 114 hours Lumbar puncture to exclude haemorrhage (or brain scintogram)
Interventions	Rx: aminophylline (Teofyllamin ACO) iv, loading dose 230 mg followed by continuous infusion 0.5 mg/kg/h in 5.5% glucose for 72 hours (22 patients) Pl: 5.5% glucose (24 patients) Duration: 3 days
Outcomes	Neurological assessments (scales: Mathew, Geismar 1976) Assessment at 1, 2, 3, 4, 10 days and discharge (average discharge 3 weeks) Death or deterioration at 3 weeks
Notes	Ex: known cerebral haemorrhage, deep coma FU: discharge
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Geismar 1976

Methods	Randomisation by coded numbered boxes prepared by hospital pharmacist Double-blind, placebo controlled 6 lost to FU, 3 in each of the treatment and control groups Single centre trial
Participants	Denmark 39 Male, 40 Female Mean age 73 years Enrolment within 96 hours

Geismar 1976 (Continued)

Lumbar puncture to exclude haemorrhage (in two-thirds of patients)

Interventions	Rx: aminophylline iv bolus 10 ml 2% solution in saline (200 mg) infused over 2 minutes after initial evaluation followed by 10 ml at 3 hours and 10 ml at 6 hours (40 patients) Pl: Physiological saline (39 patients)
Outcomes	Neurological assessment (own scale, Geismar 1976) Disability (scale: Rankin) Death or disability, length of stay, discharge deterioration at 3 weeks
Notes	Ex: myocardial infarction, renal failure, on xanthines, dextran, dexamethasone, anticoagulants FU: 3 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ex: exclusion
FU: follow up
Pl: placebo
Rx: treatment

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Dada 1971	60 patients with TIA or ischaemic stroke; follow up at 30 months Excluded: (1) pseudo-randomised trial of xanthinol nicotinate administered in one centre, control given in 4 centres; (2) timing of treatment after stroke unclear
Jenkinson 1998	20 patients post ischaemic stroke given caffeine (250 mg) or matching placebo Middle cerebral blood velocity (transcranial doppler) and blood pressure measured before and after treatment Excluded: (1) randomised crossover trial; (2) no relevant outcome measures; (3) treatment given 2 to 10 weeks post stroke
Molnar 1979	10 patients with stroke, type not given CSF and blood glucose, pyruvate, lactate, Na ⁺ , K ⁺ , Ca ⁺⁺ , Mg ⁺⁺ , Cl ⁻ and pH measured before and after infusion Excluded: (1) confounded comparison of vinpocetine ('Cavinton') and xanthinol nicotinate ('Xavin'); (2) no relevant outcome measures; (3) timing of treatment after stroke unclear
Piriyawat 2003	23 patients with acute (less than 6 hours) ischaemic stroke; follow up at discharge Excluded: (1) confounded dose-escalation trial of combined caffeine and ethanol (caffeinol); (2) not randomised; (3) no control group
Ragab 2000	19 patients post ischaemic stroke (and 10 volunteers) given caffeine (250 mg) or matching placebo Middle cerebral blood flow (xenon clearance) and velocity (transcranial doppler) measured before and after treatment Excluded: (1) randomised crossover trial; (2) no relevant outcome measures; (3) treatment given 2 to 10 weeks post stroke
Tesseris 1975	60 patients with prior cerebrovascular disease or brain trauma given vincamin ('Pervincamine'; 15 mg ia, iv or im; n = 36), aminophylline (250 mg iv; n = 12) or control (n = 12) Blood glucose, oxygen consumption, pCO ₂ and blood pressure measured after drug

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Study	Reason for exclusion
	Excluded: (1) no relevant outcome measure; (2) timing of treatment after stroke unclear; (3) status of randomisation unclear

DATA AND ANALYSES

Comparison 1. Theophylline or analogue vs control in acute ischaemic stroke: all trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death, early (≤ 4 weeks)	2	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.49, 2.56]
1.1 aminophylline	2	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.49, 2.56]
2 Death or deterioration, early (≤ 4 weeks)	2	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.41, 1.88]
2.1 aminophylline	2	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.41, 1.88]
3 Death or disability at end of follow-up	1	73	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.24, 1.68]
3.1 aminophylline	1	73	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.24, 1.68]

Analysis 1.1. Comparison 1 Theophylline or analogue vs control in acute ischaemic stroke: all trials, Outcome 1 Death, early (≤ 4 weeks).

Analysis 1.2. Comparison 1 Theophylline or analogue vs control in acute ischaemic stroke: all trials, Outcome 2 Death or deterioration, early (<= 4 weeks).

Analysis 1.3. Comparison 1 Theophylline or analogue vs control in acute ischaemic stroke: all trials, Outcome 3 Death or disability at end of follow-up.

WHAT'S NEW

Date	Event	Description
8 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 3, 1996

Date	Event	Description
15 March 2004	New search has been performed	November 2003 (1) Search strategy section updated. (2) Six studies (all excluded) added. NOTE: This review covers an area where no active research is taking place. It will be updated if relevant information becomes available.

CONTRIBUTIONS OF AUTHORS

Philip Bath conceived and designed the review; developed the search strategy; undertook interpretation of the data; wrote and updated the review; and is the guarantor of the review.

I thank Mr AA Mohiuddin and Dr FJ Bath who contributed to and co-authored earlier versions of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- South Thames NHSE, UK.
- Wolfson Foundation, UK.
- Stroke Association, UK.

NOTES

NOTE: This review covers an area where no active research is taking place. It will be updated if relevant information becomes available.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminophylline [*therapeutic use]; Brain Ischemia [drug therapy]; Caffeine [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy]; Theophylline [*therapeutic use]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans