Cochrane corner: Adenosine versus intravenous calcium channel antagonists for supraventricular tachycardia

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INTRODUCTION

Supraventricular tachycardia (SVT) is the most common cardiac cause of sustained palpitations. It affects 2 in 1000 adults and is a frequent cause of referral to cardiology services, both as an outpatient and acutely during an attack [1]. Since 1992, clinical guidelines have favoured Adenosine [2] as a first line treatment of SVT in the acute setting instead of voltage-dependent calcium channel antagonists (CCA; Verapamil or Diltiazem). However, Adenosine is associated with frequent and unpleasant adverse effects including anxiety, confusion and even a sensation of impending death. These effects, though transient, can be highly distressing; it is not uncommon to encounter patients who are reluctant to receive Adenosine due to such effects. Furthermore, Adenosine is considerably more expensive than CCA, which has implications for many healthcare providers worldwide. Therefore, despite the effectiveness of Adenosine, its primacy in the management of SVT in the UK should not prevent examination of alternative treatments, and several trials have compared the performance of Adenosine against CCA.

We therefore performed a Cochrane systematic review update [3] to incorporate new trials performed since a previous review in 2006 [4]. The review compared the effects of adenosine versus CCAs in terminating SVT (Table 1).

Table 1 PICO summary

Population	People with spontaneous SVT
Intervention	Intravenous adenosine
Comparison	Intravenous CCA

Outcome (CCA vs adenosine)	❖ Reversion rate to sinus rhythm: 92.9% (CCA) vs 89.7% (Adenosine); OR 1.51, 95% CI 0.85 to 2.68; participants = 622; studies = 7 (Figure 1) ❖ Major adverse events*: 0.66% vs 0%; OR 3.09, 95% CI 0.12 to 76.71; participants = 306; studies = 3 ❖ Minor adverse events ➢ Chest tightness: 0% vs 11.7%; OR 0.09, 95% CI 0.02 to 0.50; participants = 222; studies = 3 ➢ Flushing: 0% vs 1.5%; OR 0.01, 95% CI 0.00 to 0.24; participants = 50; studies = 1 ➢ Shortness of breath: 1.2% vs 6.9%; OR 0.23, 95% CI 0.04 to 1.37; participants = 171; studies = 2 ❖ Relapse rate: 1.14% vs 3.3%; OR 0.38, 95% CI 0.09 to 1.69; participants = 358; studies = 4 ❖ Time to effect: average 394 seconds vs 44 seconds ❖ Patient satisfaction: not reported

PICO, participants, intervention, comparison, outcome. SVT, supraventricular tachycardia. CCA, calcium channel antagonist. OR, odds ratio. CI, confidence interval.
* hypotension (n=1)

MAIN RESULTS

Our updated review identified two new randomised controlled trials (RCTs) and excluded three previously included studies, bringing the total to 7 trials recruiting 622 participants. The excluded studies included participants with SVTs induced during invasive electrophysiology studies which we deemed to be less clinically relevant to the acute presentation of a spontaneous SVT.

The trials we included used intravenous (IV) adenosine 6 mg or the equivalent of adenosine triphosphate and followed this up with another dose of 12 mg if SVT was not terminated with the first dose.
Verapamil was given in 5 mg boluses or infusion over up to 5 minutes. Diltiazem was only examined in one trial and was given by slow IV infusion at a rate of 2.5 mg/minute, to a maximum dose of 50 mg.

Our analysis found no significant difference between adenosine and CCA in either successful termination, relapse rate or major adverse events. The only major adverse event in adults was hypotension with one episode reported in the CCA group compared to none in the adenosine group. The only paediatric study included, published in the 1980s, reported two cardiac arrests with verapamil in clinical circumstances in which verapamil is not recommended in current practice guidelines; one child was receiving concomitant beta-blocker treatment and the other had cyanotic heart disease with electrolyte disturbance. Only three trials reported minor adverse events of chest tightness, nausea, shortness of breath, headache, and flushing. Chest tightness and flushing were more frequent in adenosine than verapamil. No difference was demonstrated in shortness of breath. The remaining minor adverse events could not be pooled due to heterogeneity. A pooled estimate of total minor adverse was not possible as the number of specific adverse events were reported instead of the number of people experiencing them.
Average time to reversion was less than 1 minute with adenosine and 6 minutes with

verapamil. However, results could not be pooled due to heterogeneity between studies. None of the included studies reported patients' preferences.

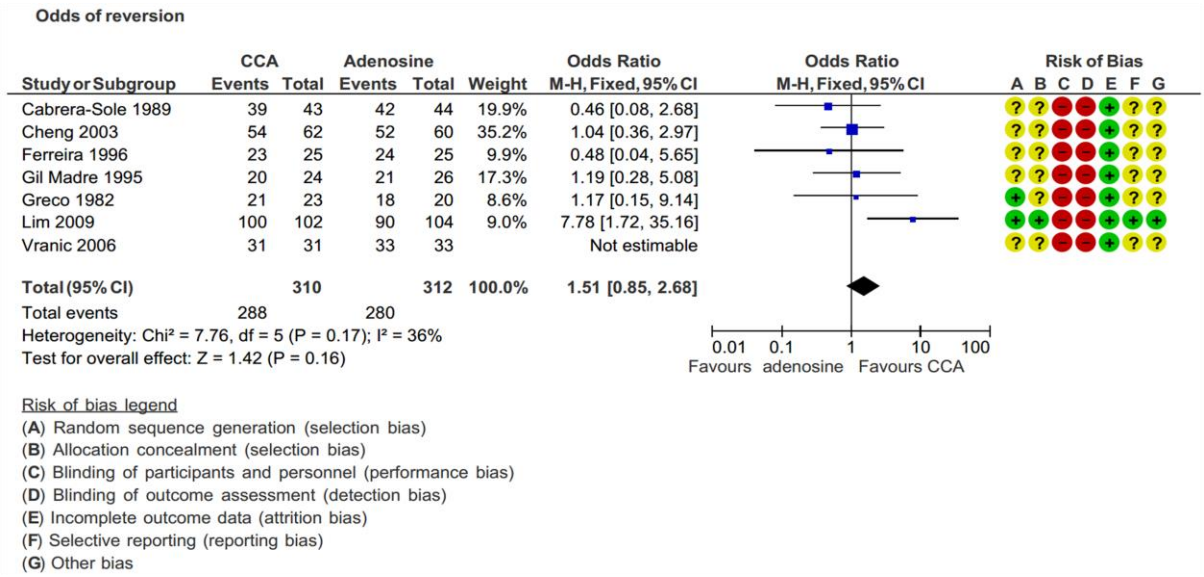

Figure 1: Meta-analysis of odds ratios of reversion to sinus rhythm

LIMITATIONS OF THE EVIDENCE

The quality of the evidence was moderate for odds of reversion and low for major adverse events based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach .
All included studies were RCTs, however, only two adequately reported the randomisation process and just one described allocation concealment. Four of the seven included studies had a crossover design; however only pre-crossover data was presented in the review. None of the included studies were blinded, however, this was not thought to have impacted the reversion rate outcome as it was objectively assessed by electrocardiogram (ECG).

Only a small number of studies reported minor adverse events. The minor adverse events were not prospectively specified and relied on post-hoc reporting that may have underestimated the actual rate. In addition, patient's experience was not reported. While adverse events might be minor and short-lived from a medical perspective, such effects may be more likely to influence preference for a particular drug, especially as many sufferers of SVTs experience recurrent attacks requiring acute termination.

CLINICAL IMPLICATIONS

The evidence does not show any superiority of adenosine vs. CCA to support the firstline use of Adenosine, as recommended by current guidelines [5,6]. Future versions of these guidelines might want to consider our new analysis in their updates.
When one of the two drugs is contraindicated, the other drug becomes the obvious first choice. Adenosine is the safer option in poor left ventricular function, concomitant beta-blocker use or suspicion of of other tachyarrhythmias such as broad complex tachycardia. Verapamil is suggested in asthmatics, previous unpleasant experience with adenosine,

people with frequent relapses on adenosine, and in people with frequent atrial or ventricular ectopics at risk of an early recurrence of the arrhythmia.

Treatment costs may be crucial in some settings. Costs were not examined in our review and only one included study reported costs. The cost of 6 mg adenosine in a Singaporean study from 2009 was $12 compared to $1 for verapamil. The total cost of sinus rhythm reversion was $23.5 for adenosine compared to $10 for verapamil [7]. This translates roughly to $12 saved per sinus rhythm restored using verapamil as opposed to adenosine, taking into account time to reversion. In the UK, the cost of 6 mg adenosine is £10 compared to £1 for 5 mg of verapamil [8]. Our review found that repeated doses were more likely to be required with adenosine (43%) compared to verapamil (26%), which further increases the total cost of treatment with adenosine.

In conclusion, both adenosine and verapamil have similar reversion rates and are readily available and simple to administer. Adenosine acts faster but has more frequent minor adverse events and is more expensive. Future research should take into account patient preference and treatment costs as these might be the only crucial differences between the two drugs.

Competing interests
None.

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