Extracts from "Clinical Evidence"

Malaria: prevention in travellers

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Interventions

Beneficial:
Insecticide treated nets

Likely to be beneficial:
Air conditioning and electric fans
Mosquito coils and vaporising mats
Smoke
Insecticide treated clothing
Protective clothing
Topical insect repellents
Doxycycline in adults
Mefloquine
Antimalaria drugs for airline pilots

Unknown effectiveness:
Aerosol insecticides
Biological control measures
Insect buzzers and electrocuters
Chloroquine
Chloroquine plus proguanil
Atovaquone plus proguanil
Pyrimethamine plus dapsone
Vaccines
Antimalaria interventions in pregnant women

Likely to be ineffective or harmful:
Amodiaquine
Sulfadoxine plus pyrimethamine
Insect repellants containing diethyltoluamide or doxycycline in children

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Background

Definition Malaria is caused by a protozoan infection of red blood cells with one of four species of the genus plasmodium: *P falciparum*, *P vivax*, *P ovale*, or *P malariae*.[1] Clinically, malaria may present in different ways, but it is usually characterised by fever (which may be swinging), tachycardia, rigors, and sweating. Anaemia, hepatosplenomegaly, cerebral involvement, renal failure, and shock may occur.
Incidence/prevalence Each year there are 300-500 million clinical cases of malaria. About 40% of the world's population is at risk of acquiring the disease.[2 3] Each year 25-30 million people from non-tropical countries visit areas in which malaria is endemic,[4] of whom between 10 000 and 30 000 contract malaria.[5]
Aetiology/risk factors Malaria is mainly a rural disease, requiring standing water nearby. It is transmitted by bites[6] from infected female anopheline mosquitoes,[7] mainly at dusk and during the night.[1 8] In cities, mosquito bites are usually from female culicene mosquitoes, which are not vectors of malaria.[9] Malaria is resurgent in most tropical countries and the risk to travellers is increasing.[10]
Prognosis Ninety per cent of travellers who contract malaria do not become ill until after they return home.[5] "Imported malaria" is easily treated if diagnosed promptly, and it follows a serious course in only about 12% of people.[11 12] The most severe form of the disease is cerebral malaria, with a case fatality rate in adult travellers of 2-6%,[3] mainly because of delays in diagnosis.[5]
Aims To reduce the risk of infection; to prevent illness and death.
Outcomes Rates of malarial illness and death, and adverse effects of treatment. Proxy measures include number of mosquito bites and number of mosquitoes in indoor areas. We found limited evidence linking number of mosquito bites and risk of malaria.[13]
Methods *Clinical Evidence* search and appraisal in November 1999. We reviewed all identified systematic reviews and randomised controlled trials (RCTs).

Question: What are the effects of non-drug preventive interventions in adult travellers?

Option: Aerosol insecticides

We found insufficient evidence on the effects of aerosol insecticides in travellers.

Benefits
We found no systematic review or RCTs. We found one questionnaire based survey of 89 617 European tourists returning from east Africa, which found no evidence that commercially available personal aerosol insecticides alone significantly reduced the incidence of malaria (P = 0.55).[14]

Harms
We found no reports of adverse effects.

Comment
None.

Option: Biological control measures

We found no good evidence for the effectiveness of biological control measures in preventing malaria, nor evidence of harm.

Benefits
We found no systematic review or RCTs. Observational studies based on mosquito counts have found no evidence that growing the citrosa plant and encouraging natural predation of insects by erecting bird or bat houses reduce bites to humans from infected anopheline mosquitoes.[14]

Harms
We found no evidence of harm.

Comment
The only known way to reduce the number of mosquitoes naturally is to eliminate sources of standing water, such as tree stump holes, and discarded tyres, cans, and bottles.[15]

Option: Air conditioning and electric fans

One large observational study in travellers found that air conditioning reduced the incidence of malaria. One small observational study found that electric fans reduced numbers of mosquitoes in indoor spaces.

Benefits
We found no systematic review or RCTs. One questionnaire based survey of 89 617 European tourists returning from east Africa found that sleeping in an air conditioned room significantly reduced the incidence of malaria ($P = 0.04$).[14] One observational study of various antimosquito interventions in six experimental huts in villages in Pakistan found that fans significantly reduced catches of culicene mosquitoes ($P < 0.05$) but did not significantly reduce catches of blood fed anopheline mosquitoes.[16]

Harms
We found no evidence of harm.

Comment
These studies support the finding that mosquitoes are reluctant to fly in windy conditions.[17]

Option: Insect buzzers and electrocuters

We found little evidence for the effectiveness of insect electrocuters and ultrasonic buzzers in preventing malaria.

Benefits
We found no systematic review and no RCTs with malarial illness as an outcome. Observational studies have found no evidence that insect electrocuters and ultrasonic buzzers reduce bites to humans from infected anopheline mosquitoes.[18 19]

Harms
We found no evidence of harm.

Comment
See biological control measures.

Option: Mosquito coils and vaporising mats

One RCT of coils and one observational study of pyrethroid vaporising mats found that these devices reduced numbers of mosquitoes in indoor spaces.

Benefits
We found no systematic review and no RCTs that used malarial illness as an outcome. We found one RCT in 18 houses in Malaysia of various mosquito coil formulations that found coils reduced populations of culicene mosquitoes by 75%.[20] One observational study of pyrethroid vaporising mats in six experimental huts in a village setting in Pakistan found that the mats reduced total catches of blood fed anopheline mosquitoes by 56%.[15]

Harms
We found no evidence of harm.

Comment
None.

Option: Smoke

One controlled trial found that smoke acted as a cheap and effective means of repelling mosquitoes during the evening.

Benefits
We found no systematic review and no RCTs that used malarial illness as an outcome. One controlled trial, in which five small fires were tended on five successive evenings in a village in Papua New Guinea, found a smoke specific and species specific effect from different types of smoke. Catches of one anopheline species were reduced by 84% through burning betelnut (95% confidence interval 62% to 94%), by 69% through burning ginger (25% to 87%), and by 66% through burning coconut husks (17% to 86%).[21]

Harms
There may be an irritant and toxic effect of smoke on the eyes and respiratory system, but this effect was not quantified.[21]

Comment
None.

Option: Insecticide treated nets

One systematic review of RCTs has found that nets treated with insecticide prevent malaria and reduce overall mortality.

Benefits
We found a systematic review which identified 18 RCTs in malaria endemic settings (non-traveller participants).[22] It found that nets sprayed or impregnated with permethrin reduced the number of mild episodes of malaria (absolute risk reduction 39%; 27% to 48%) and child mortality (relative risk of death compared with no nets or untreated nets 0.83; 0.77 to 0.90; number needed to treat 180).

Harms
Permethrin is an odourless synthetic pyrethroid with low toxicity in mammals.[15 23] It is poorly absorbed by the skin and rapidly inactivated by ester hydrolysis.[24]

Comment
Permethrin remains active for about four months.[6]

Option: Insecticide treated clothing

One trial found that clothing treated with insecticide reduced the risk of bites.

Benefits
We found no systematic review and no RCTs that used malarial illness as an outcome. One small, non-randomised controlled trial in eight US air force recruits found that permethrin treated uniforms significantly reduced the risk of mosquito bites over eight hours (relative risk reduction 93%, $P<0.01$). Adding a topical repellent containing diethyltoluamide further reduced the risk of mosquito bites (relative risk reduction 99.9%, $P<0.01$).[25]

Harms
Permethrin: See text. ***Diethyltoluamide:*** See text.

Comment
None.

Option: Lifestyle change

One observational study in travellers found that wearing trousers and long sleeved shirts prevented malaria.

Benefits
We found no systematic review or RCTs. ***Clothing:*** We found one questionnaire based survey of 89 617 European tourists returning from East Africa, which found that wearing long sleeved shirts and trousers significantly reduced the incidence of malaria ($P=0.02$).[14] ***Other lifestyle changes:*** We found no studies (see comment below).

Harms
None.

Comment
Lifestyle change implies not travelling to regions where malaria is endemic during the rainy season (when most malaria transmission occurs), and not going out of doors in the evening or at night. Travellers who take day trips from a malaria free city to a malarious region may be at minimal risk if they return to the city before dusk.[26] It would seem sensible to wear long sleeved shirts and trousers at dusk and to wear light rather than dark colours, as insects prefer landing on dark surfaces.[9]

Option: Topical insect repellents

One RCT found that an insect repellent soap reduced the number of insect bites.

Benefits
We found no systematic review and no RCTs using malarial illness as an outcome. One small RCT (eight people in a Colombian forest setting) compared repellent soap (20% diethyltoluamide and 0.5% permethrin) and placebo soap and found that repellent soap reduced the numbers of sand fly bites at four and eight hours ($P<0.05$).[27] ***Combined with insecticide treated clothing:*** See text.

Harms
We found a case series of systemic toxic reactions (confusion, irritability, insomnia) in US National Park employees after repeated and prolonged use of diethyltoluamide.[28] We found 14 case reports of contact urticaria and of irritant contact dermatitis (mostly in soldiers) as a result of diethyltoluamide.[15] The antecubital fossa seems especially at risk if diethyltoluamide is left overnight.[29] Diethyltoluamide may be harmful to children under 8 years if applied in excessive amounts (see text). It also attacks certain plastics, such as spectacle frames.[30]

Comment
Diethyltoluamide is a broad spectrum repellent effective against mosquitoes, biting flies, chiggers, fleas, and ticks[15]; it has been used for 40 years. RCTs are needed to compare diethyltoluamide with other topical repellents and placebo in preventing malaria.

Question: What are the effects of drug prophylaxis in adult travellers?

Option: Chloroquine

We found insufficient evidence on the effects of chloroquine prophylaxis in travellers.

Benefits
We found no systematic review. We found one RCT comparing chloroquine with sulfadoxine plus pyrimethamine in 173 Austrian industrial workers based in Nigeria.[31] It found no evidence of a difference in the incidence of malaria.

Harms
We found no large cohort studies in travellers. In one RCT, the commonest reported symptom with chloroquine was insomnia, occurring in 3% of people.[31] Retrospective questionnaire surveys suggest that severe adverse effects are rare at prophylactic dosages.[32]

Comment
Most drug trials have been in soldiers, and the trial results may not be generalisable to tourists or business travellers.[33 34] Alcohol consumption, other medication, and comorbidities can modify the effects of antimalaria drugs.[35 36]

Option: Chloroquine plus proguanil

RCTs found no evidence that chloroquine plus proguanil is more effective than proguanil alone or than chloroquine plus other antimalaria drugs.

Benefits
We found no systematic review. We found two RCTs in travellers. One open label RCT in Scandinavian travellers to East Africa found no significant difference in rates of *P falciparum* infection between groups (4 *v* 3 cases of *P falciparum* malaria in 384 and 383 travellers using chloroquine plus proguanil versus chloroquine and sulfadoxine plus pyrimethamine).[37] ***Versus proguanil alone:*** The second RCT, in Dutch travellers to Africa, found no significant difference in incidence of *P falciparum* malaria with chloroquine plus proguanil compared with proguanil alone.[38]

Harms
In one RCT in Scandinavian travellers, adverse effects associated with chloroquine plus proguanil were

nausea (3%), diarrhoea (2%), and dizziness (1%).[31] One cohort study in 470 British soldiers in Belize found that the risk of mouth ulcers almost doubled with chloroquine plus proguanil compared with proguanil alone (relative risk 1.9, P = 0.025).[39]

Comment
None.

Option: Doxycycline

One RCT in soldiers found doxycycline to be effective. Short term adverse effects, including skin reactions and nausea and vomiting, were reported in up to 40% of people with malaria. We found no evidence on long term safety.

Benefits
We found no systematic review. One RCT (204 Indonesian soldiers) found 1/67 cases of malaria with doxycycline versus 53/69 cases with placebo (relative risk reduction 99%; 86% to 100%).[40] One RCT (300 Indonesian adults with limited immunity) found 96.3% protective efficacy relative to placebo against falciparum malaria (85.4% to 99.6%) and 98% protective efficacy relative to placebo against vivax malaria (88% to 99.9%).[41]

Harms
In one RCT in soldiers, commonly reported adverse effects were unspecified dermatological problems (33%), cough (31%), and headache (16%).[40] One questionnaire survey (383 returned Australian travellers) found that 40% reported nausea or vomiting, 12% reported diarrhoea, and 9% of female travellers reported vaginitis.[42] Evidence from case reports suggests that up to 50% of travellers using doxycycline may experience photoallergic skin rash in sunny conditions.[43]

Comment
None.

Option: Mefloquine

One systematic review of RCTs has found that mefloquine is effective in preventing malaria. We found no good evidence that reliably attributes serious adverse reactions to mefloquine.

Benefits
We found one systematic review, which identified five RCTs in travellers (all soldiers).[44] Only one placebo controlled trial, in 204 Indonesian soldiers, assessed the protective efficacy of mefloquine in a malaria endemic setting.[40] It found that in an area of drug resistance, mefloquine had a protective efficacy of 100% (93% to 100%) in preventing malaria.

Harms
The review found no significant difference in the rate of withdrawals from mefloquine compared with other drug treatments.[44] Commonly reported adverse effects associated with mefloquine were headache (16%), insomnia (15%), and fatigue (8%).[44] Retrospective questionnaire surveys in tourists and business travellers found that sleep disturbance and psychosis were common.[45 46] One review of 74 dermatological case reports found that up to 30% of mefloquine users developed a maculopapular rash and 4-10% had pruritus.[47] Seven observational studies in tourists found that women tolerated mefloquine less well than men.[42 46 48–52] One retrospective questionnaire survey of 93 668 European travellers to East Africa found that elderly travellers tolerated mefloquine better than younger travellers ($P < 0.05$).[53] There have been several large cohort studies of mefloquine use in tourists, but none of sufficient rigour to prove that reported adverse effects are caused by the drug.[54 55]

Comment
None.

Option: Other antimalaria drugs

We found insufficient evidence on the effects of other antimalaria drugs in travellers.

Benefits
We found no systematic review. ***Sulfadoxine plus pyrimethamine:*** One open label RCT in 767 Scandinavian travellers to East Africa found no significant difference in rates of falciparum malaria between a combination of chloroquine plus sulfadoxine-pyrimethamine compared with chloroquine plus proguanil.[37] ***Amodiaquine:*** We found no RCTs in travellers. ***Atovaquone plus proguanil:*** We found no RCTs in travellers. ***Pyrimethamine plus dapsone:*** We found no RCTs in travellers. One RCT in Thai soldiers comparing a combination of pyrimethamine and dapsone with a combination of proguanil and dapsone found no significant differences in *P falciparum* infection rates over 40 days.[56]

Harms
Sulfadoxine plus pyrimethamine: One retrospective cohort study in 182 300 American travellers taking prophylactic sulfadoxine plus pyrimethamine reported severe cutaneous reactions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) in 1 per 5000-8000 users, with a mortality of about 1 per 11 000-25 000 users.[57] ***Amodiaquine:*** One retrospective cohort study in 10 000 British travellers taking prophylactic amodiaquine reported severe neutropenia in about 1 per 2000 users.[58] We found 28 case reports describing liver damage or hepatitis in travellers who had taken amodiaquine to treat or prevent malaria.[59–64] ***Atovaquone plus proguanil:*** We found no evidence of adverse effects in travellers. ***Pyrimethamine plus dapsone:*** One RCT in Thai soldiers found that fewer than 2% reported any drug related symptoms from pyrimethamine plus dapsone.[65] One retrospective cohort study in 15 000 Swedish travellers taking pyrimethamine plus dapsone reported agranulocytosis in about 1/2000 users.[57]

Comment
None.

Question: What are the effects of antimalaria vaccines in travellers?

We found insufficient evidence on the effects of antimalaria vaccines in travellers.

Benefits
We found no systematic review or RCTs of antimalaria vaccines in travellers. One systematic review identified 12 RCTs in residents of malaria endemic areas. It

found that only the SPf66 vaccine reduced first attacks of *P falciparum* malaria (odds ratio 0.80; 0.71 to 0.90).[66]

Harms
In all but one of the trials of SPf66, fewer than 10% of recipients reported a systemic reaction (fever, headache, gastric symptoms, muscle pain, dizziness), and fewer than 35% reported a local reaction (inflammation, nodules, pain, erythema, pruritis, induration, injection site warmth).[66] The remaining trial found a larger proportion of local cutaneous reactions, although these resolved within 24 hours with symptomatic treatment. It also reported higher systemic reaction rates after vaccination (11-16%), although rates after placebo were also higher (10-13%). Surveillance was also more intense than in the other trials.

Comment
None.

Question: What are the effects of preventing malaria in specific groups of travellers: children, pregnant women, and airline pilots?

Option: In children

We found insufficient evidence on the effects of antimalaria interventions in child travellers. Case reports in young children have found serious adverse effects with diethyltoluamide when used excessively and with doxycycline. It is not clear which topical insect repellents are safe in children.

Benefits
We found no systematic review or RCTs evaluating antimalaria interventions in child travellers.

Harms
We found little evidence in child travellers. ***Diethyltoluamide:*** We found 13 case reports of encephalopathic toxicity in children aged under 8 years after excessive use of topical insect repellents containing diethyltoluamide.[67 68] ***Doxycycline:*** Case reports have found that doxycycline inhibits bone growth and discolours teeth in children aged under 12 years.[9 32] ***Mefloquine:*** Three RCTs of mefloquine treatment found that children tolerate higher doses of this drug than adults.[69–71]

Comment
Infants and young children have thinner skin and a greater ratio of surface area to mass.[72] Some authors advise that ethylhexanediol should be used as a topical insect repellent in preference to diethyltoluamide in children aged 1-8 years, and that in infants, only plant based topical repellents such as citronella oil are safe.[73] However, we found insufficient evidence about the effects of these alternative repellents.

Option: In pregnant women

We found insufficient evidence on the effects of antimalaria interventions in pregnant women travellers. It is unclear which topical insect repellents are safe in pregnancy. One RCT found chloroquine to be safe in pregnancy, although its power was too low to rule out rare adverse effects. The safety of mefloquine in pregnancy has not been established.

Benefits
We found no systematic review or RCTs of antimalaria interventions in pregnant women travellers. ***Insecticide treated nets:*** We found one RCT of permethrin treated nets in 341 pregnant women living in Thailand.[74] It found that treated nets reduced the incidence of malaria in pregnancy from 56% to 33% (relative risk 1.67; 1.07 to 2.61).[75] ***Drugs:*** We found one systematic review, which identified 15 RCTs of antimalarial drugs in pregnancy, all in residents of malaria endemic settings.[76] It found no significant difference in the number of perinatal deaths or preterm births. However, it found fewer episodes of fever during the first pregnancy (odds ratio 0.36; 0.15 to 0.86) and higher birth weight in the infants (odds ratio 0.53; 0.32 to 0.81).[76]

Harms
We found little evidence relating to pregnant women travellers. ***Insecticide treated nets:*** The trial of permethrin treated nets in Thailand found no evidence of toxic effects to mother or fetus.[75] ***Topical insect repellents:*** Some, but not all, animal studies have found that diethyltoluamide crosses the placental barrier.[77] Animal studies of reproductive effects of diethyltoluamide have conflicting results.[78 79] We found one case report indicating an adverse fetal outcome (mental retardation, impaired sensorimotor coordination, craniofacial dysmorphology) in a child whose mother had applied diethyltoluamide daily throughout her pregnancy.[80] ***Chloroquine:*** One RCT in 1464 long term residents of Burkina Faso found no adverse effects in pregnant women.[74] ***Doxycycline:*** Case reports have found that doxycycline taken in pregnancy or while breast feeding may damage fetal or infant bones or teeth.[9 32] ***Mefloquine:*** One placebo controlled RCT in 339 long term residents in Thailand found more reports of dizziness with mefloquine than placebo (28% *v* 14%, $P<0.005$) but no other significant adverse effects on the mother, the pregnancy, or on infant survival or development over two years of follow up.[81]

Comment
Pregnant women are relatively immunosuppressed and are at greater risk of malaria than non-pregnant women.[82] Contracting malaria significantly increases the likelihood of losing the fetus.[78] Because of a theoretical risk of mutagenicity from diethyltoluamide, some authors advise that only plant based topical insect repellents such as citronella oil are safe in pregnancy.[73] However, we found insufficient evidence on the effects of this alternative repellent. Mefloquine is secreted in small quantities in breast milk, but it is believed that levels are too low to harm infants.[32]

Option: In airline pilots

We found insufficient evidence about the effects of antimalaria drugs in airline pilots.

Benefits
We found no systematic review or RCTs.

Harms
Doxycycline: One retrospective questionnaire survey of 28 Israeli pilots found that 39% experienced adverse effects from doxycycline (abdominal pain

7/28, fatigue 5/28).[83] ***Mefloquine:*** One placebo controlled RCT in 23 trainee commercial pilots found no evidence that mefloquine significantly affected flying performance (mean total number of errors recorded by the instrument coordination analyser 12.6 with mefloquine *v* 11.7 with placebo).[84] One retrospective questionnaire survey of 15 Israeli non-aviator aircrew found that 13% experienced adverse effects from mefloquine (dizziness, nausea, and abdominal pain in 2/15, abdominal discomfort in 1/15).[83]

Comment

None.

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Lesson of the week

Unrecognised accidental overdose with diltiazem

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Invasive haemodynamic monitoring should be considered when hypotension fails to respond to empirical treatments

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We present a potentially fatal case of diltiazem overdose caused by inappropriate self treatment. We highlight the clinical features of diltiazem overdose, relevant haemodynamic findings, and treatment options.

Case report

A 54 year old white man presented with nausea, dizziness, and collapse after an episode of severe angina 10 hours previously. He had been free of pain for 8 hours but was bradycardic and hypotensive and had severe pulmonary oedema. He had no features suggestive of ongoing infection. Maintenance treatment for his angina was bisoprolol 5 mg once daily, slow release diltiazem 180 mg twice daily, isosorbide mononitrate 40 mg three times a day, nicorandil 10 mg twice daily, frusemide 40 mg once daily, simvastatin 20 mg once daily, fluoxetine 40 mg once daily, and aspirin 75 mg once daily. He was known to have severe triple vessel coronary artery disease and poor left ventricular function. Electrocardiography indicated a sinus bradycardia with new first degree heart block (PR interval 300 milliseconds), pre-existing left bundle branch block, and no new changes in the ST segments or T waves suggestive of an acute myocardial infarction.[1] Despite treatment for cardiogenic shock with intravenous dopamine, dobutamine, and diuretics, he developed acidosis, anuria, type 1 respiratory failure, and persistent hypotension. As there was no electrocardiographic or enzymatic evidence of myocardial infarction, he was transferred to Papworth Hospital for consideration of coronary artery bypass grafting as treatment for presumed ischaemic left ventricular dysfunction. On arrival, a carefully elicited history showed that his angina had resolved eight hours before his initial admission after self treatment with six 180 mg slow release diltiazem tablets at the onset of his symptoms. In the past he had successfully treated himself with four 40 mg isosorbide mononitrate tablets in a similar situation. Invasive haemodynamic monitoring with a Swan-Ganz catheter was instituted, and an intra-aortic balloon pump was inserted percutaneously by way of the right femoral artery. The table shows the results of measuring several haemodynamic variables. The history, clinical findings (inappropriate sinus bradycardia, newly developed first degree heart block), and haemodynamic data (profound vasodilation, with a normal cardiac index despite underlying poor left ventricular function and in the absence of sepsis or liver disease) suggested a diltiazem overdose. He was started on noradrenaline, titrated against the systemic vascular resistance obtained from haemodynamic monitoring. His renal, respiratory, and cardiac problems recovered to baseline levels over the next 48 hours, with normalisation of the PR interval. He was successfully weaned from all inotropic support, and the intra-aortic balloon pump was removed. His liver function test results remained normal throughout, and blood cultures gave negative results. He was transferred back to his referring hospital. Diltiazem overdose was confirmed seven weeks later. The serum concentration of diltiazem 23 hours after ingestion was 1230 ng/ml (therapeutic range 40-160 ng/ml).

Haemodynamic measurements in patient with diltiazem overdose

Haemodynamic variables	Patient data (normal range)
Cardiac index (l/min/m^2)	3.5 (2.5-4.5)
Systemic vascular resistance (dynes/s/cm^5)	438 (800-1200)
Central venous pressure (mm Hg)	15 (0-8)
Pulmonary vascular resistance (dynes/s/cm^5)	92 (<200)
Mean pulmonary artery pressure (mm Hg)	24 (10-20)
Mean pulmonary capillary wedge pressure (mm Hg)	16 (4-14)
Arterial blood pressure (mm Hg)	53 (70-105)

Discussion

Diltiazem is a calcium channel antagonist, which causes vasodilation and has negative chronotropic,