CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	203826
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Applicant's letter date:	12/28/2011
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Product:	Phenylephrine Hydrochloride
Indication:	Hypotension and Shock
Applicant:	Westward Pharmaceutical Corp.
Review Division:	Cardiorenal Products
Reviewer:	Philip J. Gatti, Ph.D.
Supervisor/Team Leader:	Albert F. DeFelice, Ph.D.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Quynh Nguyen

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1 Executive Summary

1.1 Introduction

Phenylephrine hydrochloride is a selective alpha-1 receptor adrenergic agonist which in many species including man dose-dependently and reversibly increase arterial blood pressure. The indication sought in this NDA is intravenous use in acute hypotensive states, namely, endotoxin shock and peri-operative hypotension.

1.2 Brief Discussion of Nonclinical Findings

Except for one proof of concept study in the dog, all nonclinical findings are as asserted in the published literature.

1.3 Recommendations

1.3.1 Approvability

Yes

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

TBD

2 Drug Information

2.1 Drug

CAS Registry Number
67-76-7

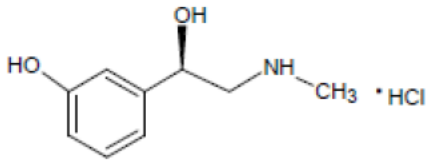
Generic Name
Phenylephrine Hydrochloride

Code Name
None

Chemical Name
(-)-m-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride

Molecular Formula/Molecular Weight
$C_9H_{13}NO_2HCl$; 203.67

Structure or Biochemical Description



Pharmacologic Class
Alpha-1 adrenergic receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Pre-IND 109977 (Nov. 2010) Sponsor was Baxter Pharmaceuticals.

2.3 Drug Formulation

Table 3.2.P.3.2-1.
Batch Formula of Phenylephrine Hydrochloride Injection, USP

Strength (Label Claim)	10 mg/mL	
Proposed Commercial Batch Size		(b) (4)
Component and Quality Standard	Quantity per 1 mL	Quantity per Batch
Phenylephrine Hydrochloride, USP	10 mg	(b) (4)
Sodium Chloride, USP	3.5 mg	
Sodium Citrate Dihydrate, USP	4 mg	
Citric Acid Monohydrate, USP	1 mg	
Sodium Metabisulfite, USP	2 mg	
Sodium Hydroxide NF (as a 10% sodium hydroxide solution)	As needed basis for pH adjustment only	
Hydrochloric Acid, NF (as a 1:10 Hydrochloric Acid solution)	As needed basis for pH adjustment only	
Water For Injection, USP		(b) (4)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

A QSAR analysis was submitted for impurities exceeding allowed amounts. These are: phenylephrone and a phenylephrine-citrate adduct (amide linkage). Results of these analyses were negative. Predictions of genotoxicity and carcinogenicity for both impurities were negative.

2.6 Proposed Clinical Population and Dosing Regimen

The agent will be administered intravenously to adults as a 10 mg/ml solution. The dose will depend on the level of hypotension that presents and the response to the

phenylephrine administered. The agent will be titrated to normotension in these hypotensive individuals.

2.7 Regulatory Background

This agent was submitted as a pre-IND in Oct.-Nov. 2010.

3 Studies Submitted

3.1 Studies Reviewed

One study in dogs as a proof of concept study will be briefly reviewed.

3.2 Studies Not Reviewed

No other studies were submitted. A review of the literature showing the pressor effect of phenylephrine in a variety of species was submitted by the sponsor. Also, toxicology studies performed by the National Toxicology Program (NTP) in 1987 is summarized in this review.

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

The following review of the literature was provided by the Sponsor:

Mouse in vitro[4-31]

Twenty-one of the 28 mouse in vitro studies were related to vasoconstriction. Phenylephrine demonstrated constriction of blood vessels (aorta, pulmonary artery, mesenteric artery, femoral artery, coronary artery or tail artery) in all 21 (100%) of the vasoconstriction-related articles.

Seven out of the 28 mouse in vitro articles (25%) were related to the inotropic effect. Three out of 7 inotropic-related articles (43%) had a negative response, and 3 out of 7 articles (43%) had a mixed response of both positive and negative phases. One out of 7 articles (14%) had a positive inotropic effect. The response to phenylephrine in ventricular myocardium of mice was shown to be different from those of larger mammals.

Rat in vitro[4, 21, 32-275,48, 276-348]

There were 246 (77%) vasoconstriction-related articles out of 319, in which phenylephrine constricted blood vessels (aorta; mesenteric, tail, saphenous, carotid, femoral, iliac, caudal, renal, pulmonary, hepatic, uterine, and basilar arteries; arterioles; vena cava; femoral, pulmonary, renal, portal and iliac veins) in all 246 articles (100%).

Seventy-four (23%) out of 319 in vitro rat articles were identified as relevant to the inotropic effect in the literature review. Phenylephrine produced an inotropic effect in 73 of 74 articles (99%).

Hamster in vitro[349]

There was 1 relevant in vitro hamster article, which demonstrated that the vasoconstrictor response to phenylephrine is unaffected by hypertension.

Other rodent in vitro[286, 350-370]

Twenty-two in vitro other rodent (guinea pig) articles were identified as relevant for supporting the primary phenylephrine pharmacodynamics parameters. Eight out of the

22 articles (36%) involved vasoconstriction. One article showed how stenosis can alter vascular reactivity in arteries distant from the injury site by either reducing or increasing the response. Phenylephrine induced vasoconstriction in 8 out of 8 articles (100%).

Fourteen out of 22 articles (64%) examined the inotropic response to phenylephrine. Phenylephrine produced a positive inotropic effect in 14 out of 14 articles (100%). A biphasic response was noted in 2 out of 14 articles (14%) and a triphasic response was observed in 1 of 14 articles (7%).

Rabbit in vitro[318, 369-431]

Sixty-four in vitro rabbit articles were identified as relevant for supporting the primary phenylephrine pharmacodynamics parameters. Forty out of 64 articles were vasoconstrictor-related (62.5%). Vasoconstriction was induced in all 40 articles (100%). One article revealed a hyporesponsiveness to phenylephrine in pregnant rabbits.

Twenty-four out of 64 rabbit articles (37.5%) were related to the inotropic response. Phenylephrine produced a positive inotropic response in 24 out of 24 articles (100%) and produced a biphasic response in 2 out of 24 articles (8%).

Dog in vitro[154, 393, 423, 432-460]

Thirty-two in vitro dog articles were identified as relevant for supporting the primary phenylephrine pharmacodynamics parameters. Phenylephrine was utilized as a vasoconstrictor in 27 out of 32 articles (84%) in the relevant literature, constricting blood vessels in 26 out of 27 articles (96%). There was 1 article (4%) in which phenylephrine did not constrict coronary arterioles.

There were 5 out of 32 articles (16%) related to the inotropic response in the literature review. Phenylephrine produced a positive inotropic effect in 5 out of 5 articles (100%). The canine heart appears to be exceptional compared to other animals; the inotropic response does not appear to be attributable to α-AR, but rather β-AR.

Nonhuman primate in vitro[461, 462]

One nonhuman primate article was identified as relevant to supporting the primary phenylephrine pharmacodynamics parameters. That article revealed that events coupling α_1-AR activation with vasoconstriction are more effective in perinatal than in adult baboons.

One inotropic response article was found to support the primary phenylephrine pharmacodynamics parameters. In the monkey (*Macaca fuscata*), α-AR and β-AR

mediate the positive inotropic response: α-AR in low phenylephrine concentration and β-AR in high phenylephrine concentration.

Human in vitro[10, 48, 262, 331, 357, 393, 463-490]

Thirty-four human in vitro articles were identified that support the primary phenylephrine pharmacodynamics parameters. Twenty-four out of 34 relevant articles (71%) were vasoconstrictor-related. Phenylephrine constricted blood vessels in 23 out of 24 articles (96%). One article (4%) showed no vasoconstrictive effect at very low concentrations (0.005 nM to 1 nM) in the umbilical vein.

Ten out of 34 relevant articles were related to the positive inotropic effect (29%). Phenylephrine produced a positive inotropic effect in 9 out of 10 articles (90%). One of these articles (10%) examined age-related effects and provided evidence for the loss of myocardial responsiveness to phenylephrine with age.

Other nonrodent mammal in vitro[393, 491-529]

Forty in vitro nonrodent mammal (ferret, sheep, pig, cow, horse, and cat) articles were identified as relevant for supporting the primary phenylephrine pharmacodynamics parameters. The vasoconstriction-related articles made up 27 out of 40 (67%) of the relevant nonrodent mammalian literature. Phenylephrine constricted blood vessels in 25 out of 27 articles (93%). In 2 of these articles (7%), phenylephrine did not constrict pulmonary resistance arteries or circumflex arteries in the pig.

The inotropic response comprised 13 out of 40 nonrodent mammal articles (32.5%). Phenylephrine induced a positive inotropic effect in 13 of 13 articles (100%). Phenylephrine produced a very small positive inotropic effect during hypoxia.

Nonmammals in vitro[530-532]

Three in vitro nonmammal articles (chick and frog) were identified as relevant for supporting the primary phenylephrine pharmacodynamics parameters. In 3 out of 3 articles (100%), phenylephrine produced a positive inotropic effect through β-AR activation.

Mouse in vivo[14, 533-541]

Nine mouse in vivo studies were identified as relevant to supporting the primary phenylephrine pharmacodynamics parameters. Phenylephrine produced a pressor or vasoconstrictor response in 9 out of 9 articles (100%). Phenylephrine-induced increase of MAP in the diabetic model was decreased compared to the control model.

Rat in vivo[81, 84, 87, 139, 199, 350, 542-614]

The literature search provided 80 articles supporting the primary phenylephrine pharmacodynamics parameters. Seventy-seven out of 80 articles (96%) examined the pressor/vasoconstrictor effect of phenylephrine in the rat, with these actions demonstrated in 77 out of 77 articles (100%). Age-related changes in the pressor response due to a decrease in the maximum number of binding sites were presented in 2 of these articles.

The inotropic effect was the subject of 3 out of 80 articles (4%), providing evidence for its positive inotropic effect in 3 out of 3 articles (100%).

Hamster in vivo[615]

The pressor/vasoconstrictor action of phenylephrine was presented in only 1 hamster article.

Rabbit in vivo[416, 421, 616-629]

Seventeen in vivo rabbit articles were identified in the literature search to support the primary phenylephrine pharmacodynamics parameters. The pressor/vasoconstrictor action of phenylephrine was demonstrated in 17 out of 17 articles (100%). Blood pressure was shown to increase in resting and hemorrhagic shock conditions.

Dog in vivo[380, 579, 630-708]

The literature search provided 81 in vivo dog articles that support the primary phenylephrine pharmacodynamics parameters. The pressor/vasoconstrictor effect of phenylephrine was examined in 79 out of 81 articles (98%), with confirmation of its action in 78 out of 79 articles (99%). Phenylephrine increased blood pressure in 9 out of 9 articles utilizing shock or shock-like states (100%).

Two out of 2 articles (100%) presented the positive inotropic effect of phenylephrine, which was able to overcome the negative inotropic action of halothane.

Nonhuman primate in vivo[709-712]

Four nonhuman primate articles were identified that support the primary pharmacodynamics parameters. The pressor/vasoconstrictor effect was seen in 4 out of 4 articles (100%).

Other nonrodent mammal in vivo[713-752]

Forty other nonrodent mammal in vivo articles were identified as supportive of the primary pharmacodynamics parameters. Thirty-eight out of 40 articles (95%) were related to the pressor/vasoconstrictor effect of phenylephrine, with the effect seen in 38 out of 38 articles (100%).

Two articles examined the positive inotropic effect of phenylephrine.

Nonmammal in vivo[753-757]

Five nonmammal in vivo articles that support the primary pharmacodynamics parameters were identified. The pressor/vasoconstrictor effect was presented in 5 out of 5 articles (100%).

Overview of Sponsor's Proof of Concept Study in Dogs

Title: Pharmacology Study to Determine the Dose-Response and Exposure Response of IV Phenylephrine in the Canine Endotoxic Shock Model

Three studies were performed by the CRO (b) (4) located in (b) (4) in Oct. and Nov. 2011 in an attempt to determine the starting dose, the dosing range for infusion and the MTD for phenylepherine in a canine model of endotoxic shock. These studies were suggested at a pre-IND meeting with the FDA in Nov. 2010. The 3 studies were:

1) Model validation of septic shock
2) Pilot IV bolus study
3) Primary IV bolus/IV infusion study

The results reported by the sponsor are provided below:

Model Validation of Septic Shock:

For the Model Validation study (*AVANZA* Study No. 2066-11124) 4 male beagle dogs were used to determine the dose of LPS needed to decrease the mean arterial blood pressure (MAP) by at least 20% from baseline, the bolus dose of phenylephrine required to increase the MAP, and the infusion rate of phenylephrine needed to maintain a stable MAP (within ± 5 mmHg) for at least 30 consecutive minutes. The animals were implanted with telemetry devices to monitor BP and heart rate, and jugular catheters to facilitate blood draws. Blood was drawn prior to initiation of baseline data recording, at the completion of each bolus dose of phenylephrine, and following each change in phenylephrine infusion rate.

The first animal was used to determine the target LPS dose to be given to the subsequent animals. The second animal was used to determine the target bolus phenylephrine dose to be given the subsequent animals and to confirm the LPS dose that would induce at least a 20% drop in MAP. Based on the results, the LPS dose required to drop the MAP by at least 20% was determined to be approximately 1.2 mg/kg and it was determined that a bolus dose of ~1.4 µg/kg phenylephrine was to be given to the next animal.

The third animal received a bolus dose of 1.456 mg/kg LPS and the MAP was observed until it had decreased by more than 20% from the baseline, which occurred 32 minutes later. After an additional 10 minutes the MAP further decreased to a maximum of 30% from baseline and then began to slowly increase. A bolus dose of 1.4 µg/kg phenylephrine was given, followed by initiation of the phenylephrine infusion one minute later at a rate of 2.5 mL/min. The MAP returned to baseline 6 minutes later and the infusion rate was decreased as necessary to maintain a stable MAP for at least 25 minutes. Based on the results, it was decided to give a higher LPS dose to the next animal to determine if the time required to decrease the MAP could be shortened.

The fourth animal was given a bolus dose of 2.887 mg/kg LPS in an effort to determine if a higher LPS dose would shorten the time required to decrease the MAP by more than 20% from the baseline. An actual decrease in MAP of 29% from baseline was observed 17 minutes after LPS administration. A bolus dose of 4.113 µg/kg phenylephrine was given (MAP had decreased to 35% from baseline by this point) followed by infusion of phenylephrine 2 minutes later at a rate of 1.94 mL/min. Three increases in infusion rate were made and the MAP returned to baseline 20 minutes from the start of the infusion. The infusion rate was adjusted as necessary to maintain a stable MAP for at least 30 minutes. Although this resulted in a shorter timeframe to effect a decrease in MAP, it resulted in a longer timeframe for the MAP to return to baseline upon administration of phenylephrine.

A model of LPS-induced septic shock was established in Beagle dogs. A single dose of LPS ranging from approximately 1.2 to 1.5 mg/kg (232,000 to 325,000 EU/kg) resulted in a 20% decrease of MAP within 32 to 36 minutes after administration of LPS; further decreases of 30 to 38% from baseline occurred after an additional 10 to 11 minutes. Administration of repeated doses of LPS provided no additive effect on lowering of the MAP. Bolus doses of phenylephrine at approximately 1.4 µg/kg followed by infusion of a 7 µg/mL solution were able to maintain the MAP at or above levels obtained during baseline with occasional adjustments to the rate of infusion.

Plasma samples collected during the LPS-induced septic shock model validation study were sent to KCAS to be used for bioanalytical method validation. A reliable method was established for the measurement of phenylephrine in dog plasma, with K_2EDTA as anticoagulant, by liquid chromatography–mass spectrometry (LC-MS/MS) in the concentration range of 0.0500 to 9.60 ng/mL (low curve) and 1.00 to 192 ng/mL (high curve).

Pilot IV Bolus Study:

For the IV bolus study (*AVANZA* Study No. 2066-11007), 5 single IV bolus doses of phenylephrine (0.15, 1.4, 4, 7, 10 μg/kg) were administered to 5 groups of randomly assigned dogs in a parallel manner. Each group contained 4 dogs (2 males and 2 females). The animals were implanted with telemetry devices to monitor BP and heart rate, and jugular vein catheters to facilitate blood draws. Blood was drawn from each animal prior to anesthesia and surgery, and at 5 (± 30 seconds), 10, 15, 20, 30, 45 minutes (± 1 minute) and 1, 1.5, 2, 3, 4, 5, and 6 hours (± 3 minutes) following administration of phenylephrine for determination of PKs. The heart rate, BP (systolic, diastolic, and mean arterial), body temperature, and electrocardiogram (ECG) waveform were continuously recorded until the 6-hour blood collection time point. BP and heart rate data were sampled at 1, 2, 3, 4, 5 (± 30 seconds), 10, 15, 20, 30, 45 minutes (± 1 minute), and 1, 1.5, 2, 3, 4, 5, and 6 hours (± 3 minutes) following administration of phenylephrine.

The animals received a dose of LPS (approximately 300,000 EU/kg) by bolus IV injection via the cephalic vein. The MAP was continuously monitored in an attempt to achieve a lowering of the MAP by at least 20% (or 30% for the first two animals dosed). If a decline in MAP by at least 20% from baseline was not achieved, the animal was euthanized without administration of phenylephrine. For the animals that failed to respond to LPS, a second dose of LPS was administered, but did not result in a lowering of the MAP by at least 20% of baseline. The response to the administration of LPS was

highly variable, and 6 of the 20 animals did not achieve at least a 20% decrease from their baseline MAP value after LPS was administered to induce shock. In some cases there was a steep drop in the MAP whereas in others there was no response to the administration of the LPS. Both sexes showed similar variable responses following LPS administration.

For the animals that responded to the administration of LPS, once the MAP had declined from the baseline by a minimum of 20% following LPS administration, a bolus dose of phenylephrine was given via the cephalic vein in one of the 5 doses listed above. The dose volume was 0.2 mL/kg.

Administration of phenylephrine resulted in a transitory rise in MAP, usually starting at 1 minute following dosing and lasting from 1 to 2 minutes. The exception was the response at the lowest dose which had minimal to no effect on MAP. In general, the MAP increased in a dose-dependent manner in response to phenylephrine administration but the responses at both 7 and 10 µg/kg were similar in magnitude. There was no apparent difference in the response of male and female dogs to administration of phenylephrine.

Following the transitory rise in MAP following administration of phenylephrine, BP and heart rate continued to decrease. The MAP often increased again to levels that were in some cases higher than those recorded prior to LPS administration before ultimately falling over the subsequent recording interval although the response varied without relationship to dose of phenylephrine. In some cases although the MAP was declining during this interval, the systolic blood pressure (SBP) remained high or increased even as the diastolic blood pressure (DBP) and heart rate were decreasing.

Analysis of the plasma samples by KCAS demonstrated the standard curve to be linear from 0.0500 to 9.60 ng/mL for phenylephrine.

Pharmacokinetic parameters were derived using noncompartmental analysis of the plasma concentration vs. time data and a validated WinNonlin™, Version 5.2 program. Plots were generated using WinNonlin 5.2 and S-plus. PD parameters were calculated using WinNonlin 5.2, and fitting of the mean effect vs. mean maximum phenylephrine plasma concentration was performed using a sigmoid E_{max} model.

Spaghetti plots of mean plasma phenylephrine concentration vs. time showed the plasma phenylephrine concentrations increase as the dose increases, and the increases appear to be dose proportional.

The lowest dose of phenylephrine (0.15 μg/kg) yielded phenylephrine plasma concentrations which were close to the limit of quantitation (LOQ). Therefore, only C_{max} and AUC_{0-t} could be determined. The results showed that the increases in mean C_{max} and AUC were relatively proportional to the increases in dose of phenylephrine. The mean half-life values of phenylephrine ranged from approximately 1 to 3 hours. The mean clearance was 19 to 25 mL/min/kg, and the mean volume of distribution ranged from 2.3 to 4.5 L/kg.

Dose proportionality was assessed using C_{max} and $AUC_{0-\infty}$, and the results indicated that there exists a positive linear relationship between dose of phenylephrine and these PK parameters.

Drug exposure appeared to act in a dose-proportional manner; however this could not be conclusively shown due to the 90% confidence interval extending outside the critical region of 0.95 to 1.05 as defined using the power model.

A total of 6 female and 8 male dogs were treated with phenylephrine, and gender did not appear to significantly affect the value of the PK parameters.

The results of this study indicate that the mean blood pressure values increased with increasing mean exposure data (dose, C_{max} and C_0) up to 7 μg/kg. The overall data fit to an E_{max} model for the 5 dose groups for all of the hemodynamic variables (SBP, DBP, MAP and heart rate). The mean heart rate decreased with increasing mean exposure of phenylephrine and followed an E_{max} model in the reverse direction as the BP variables.

Primary IV Bolus/IV Infusion Study:

For the IV Bolus/IV Infusion study (*AVANZA* Study No. 2066-11012) 16 (8/sex) Beagle dogs were randomly assigned to 2 groups (4 animals/sex in Groups 1 and 2). The animals were implanted with telemetry devices to monitor the BP and heart rate, and jugular catheters to facilitate blood draws.

Each animal received LPS at a dose of approximately 300,000 EU/kg by bolus IV injection via the cephalic vein. The heart rate and BP data were monitored, and once the MAP had declined from the baseline by at least 20%, phenylephrine or the vehicle was administered as follows:

All phenylephrine and vehicle dosing was given via the cephalic vein. For Group 1 (Control) animals, the IV infusion of the vehicle was started immediately after the vehicle bolus dose, and the dose volume for the vehicle IV infusion was 0.2 mL/kg/min throughout the entire infusion interval (up to approximately 2 hours depending on survival).

For Group 2 (phenylephrine animals), an initial bolus dose of phenylephrine (3 μg/kg) was followed by IV infusion of the phenylephrine (at an initial dose level of

3.5 μg/kg/min) as soon as the MAP started to show an increase after administration of the bolus dose. For the first Group 2 animal dosed, the initial dose volume for the phenylephrine IV infusion was 0.2 mL/kg/min and was adjusted as necessary to maintain the MAP within ± 5 mmHg of the baseline MAP. The infusion rate was adjusted as necessary by 0.05 mL/kg/min until the baseline MAP was reached. This initial infusion rate and small adjustment increment resulted in a long interval of time to reach the baseline MAP and difficulty in maintaining the MAP. Thus, the initial dose volume for the phenylephrine IV infusion for the remaining Group 2 animals was increased to 0.5 mL/kg/min and was adjusted in increments of 0.2 mL/kg/min as needed to maintain the MAP within ± 5 mmHg of the baseline MAP. Once the baseline MAP was achieved, the infusion rate was adjusted as necessary to maintain the MAP within ± 5 mmHg for at least 30 minutes and then for an additional ~2 hours, at which time the infusion was discontinued, except as noted.

For PK evaluation, blood was drawn from each animal prior to anesthesia and surgery, at 5 (± 30 seconds), 10, and 15 minutes (± 1 minute) following the bolus dose and at 0.5, 0.75, 1, 1.5, and 2 hours (± 3 minutes) following the 30-minute interval following the administration of phenylephrine. The heart rate, BP (systolic, diastolic, and mean arterial), body temperature, and ECG waveform were continuously recorded until the final blood sample was collected. BP and heart rate data were sampled at 1 minute intervals until the target BP was reached and the maintenance dose was established for 30 minutes. The heart rate and BP data was sampled from telemetry recordings at 0.5, 0.75, 1, 1.5, and 2 hours (± 3 minutes) following the 30-minute interval following the start of infusion, at 0.5, 0.75, 1, 1.5, 2, 3, and 4 hours (± 3 minutes) following the end of infusion.

Of the control animals, a single male and 3 females survived for 4 hours following the termination of the infusion of saline vehicle. The remaining female survived for 3 hours following termination of saline infusion. In the case of the single male and one of the females, the infusion of saline resulted in an increase in MAP that remained stable for the duration of the data collection interval.

The 3 other females underwent a gradual fall in MAP during the post-infusion interval whereas the drop in MAP was much faster in male animals following the termination of infusion with death occurring within minutes to 1.5 hours after completion of infusion; one died shortly after the end of the saline infusion, one after 0.5 hours of saline infusion,

and the last after 1.5 hours of saline infusion. The data suggest that there is a sex difference in the physiological response in dogs to the induction of endotoxic shock.

Similarly, a bolus dose of phenylephrine followed by infusion of phenylephrine following induction of endotoxic shock resulted in the following: one male and 3 female animals survived for 4 hours after the termination of infusion, and the remaining female survived for 3 hours following the termination of infusion. For the remaining males, one died shortly after the end of the infusion, one died 0.25 hours after the end of the infusion, and one died 2 hours after the end of infusion.

Maintenance of the MAP within ± 5 mmHg of the baseline after the baseline MAP was not achieved in all cases. In males, for the first animal, where the initial infusion rate and infusion adjustment rate was lower, the baseline MAP was never reached during the infusion period with phenylephrine. For the second and third animals, the MAP was not stable and was not able to be maintained within ± 5 mmHg of the baseline for most of the phenylephrine infusion period, but was within ± 10 mmHg of the baseline for the entire infusion period. The fourth male had a very stable MAP throughout the infusion period, except for one instance when it increased to slightly above the ± 5 mmHg range.

For the first female animal, the MAP was not stable and was not able to be maintained within ± 5 mmHg of the baseline for most of the phenylephrine infusion period, but was within ± 10 mmHg of the baseline for the entire infusion period. The remaining females had a stable MAP for most of the phenylephrine infusion, except for a few sporadic intervals when the MAP increased or decreased beyond the ± 5 mmHg range, but was within ± 10 mmHg of the baseline for the entire infusion period.

Analysis of the plasma samples by KCAS demonstrated that the assay was linear from 0.0500 to 9.60 ng/mL (low curve) with 200 µL aliquot volume and 1.00 to 192 ng/mL (high curve) with a 100 µL aliquot volume.

Results from this study indicated that administration of LPS resulted in at least a 20% drop in MAP although there was an apparent sex difference in the physiological response to this agent. Administration of saline or phenylephrine by both bolus and IV infusion following induction of shock by administration of LPS resulted in similar increases in MAP.

PK parameters were derived using noncompartmental analysis of the plasma concentration vs. time data and a validated WinNonlin™, Version 5.2 program. Plots were generated using WinNonlin 5.2 and S-plus. PD parameters were calculated using WinNonlin 5.2, and fitting of individual canine effect vs. phenylephrine plasma concentrations was performed using a sigmoid E_{max} model.

Spaghetti plots of phenylephrine plasma concentration vs. time following IV bolus plus infusion administration showed there was wide variability in the PK profile of phenylephrine. The C_{max} values ranged from as low as 79 ng/mL to a maximum of 3,360 ng/mL, and the t_{max} values ranged from 5 minutes to 210 minutes. Similar wide variability was also seen with the AUC values. This variability can be explained by the fact that the IV infusion of phenylephrine was titrated to reach a specific effect in BP. Therefore, the dose of phenylephrine was dependent on the individual response of each animal to the effects of the endotoxin as well as their individual responses to the pressor effects of phenylephrine.

The effects of both phenylephrine and placebo administration on mean hemodynamic parameters (systolic, diastolic and mean arterial blood pressure, and heart rate) were compared. The results indicated that phenylephrine caused an overall mean increase in all BP parameters. The phenylephrine-induced changes in heart rate were negligible, thus the effect of phenylephrine on heart rate could not be conclusively ascertained in this study.

An apparent inverse relationship was noted between the Area Under the Curve ($AUC_{0\rightarrow t}$) for phenylephrine and the Area Under the Effect Curve (AUEC) for BP measurements, however this relationship is an anomaly resulting from the study design that titrated the phenylephrine dose to a targeted blood pressure. Dogs that were less sensitive to the pressor effects of phenylephrine required greater doses of phenylephrine, resulting in higher AUC values, and the stepwise increase in infusion rate meant that these animals received a pharmacologically active dose later in the dosing paradigm, leading to a lower AUEC.

Reviewer's Comments

These studies were inconclusive and did not answer the questions that they were designed to answer. In summary, the model to produce endotoxic shock in the dog was highly variable. To achieve a certain level of shock and thus hypotension in these animals, a highly variable amount of endotoxin was needed. As a result, the dose of phenylephrine needed to raise the BP back to "normal" was also highly variable. Thus, it leads one to conclude that in a clinical setting, variable amounts of PE will be needed depending on the level of shock and the degree of hypotension observed. One would need to titrate the PE to the effect desired in the hospital.

4.2 Secondary Pharmacology

Provided by the Sponsor:

Mouse in vitro[758-761]

Four in vitro mouse studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Cardiomyocytes from endothelial nitric oxide synthase (eNOS) knockout (KO) mice showed excessive hypertrophy 72 hours after exposure to phenylephrine. Phenylephrine significantly stimulated proliferation of primary smooth muscle cells in the aorta and inhibited hypotonic activation of volume-regulated anion channel current in ventricular cells.

Rat in vitro[760, 762-863]

One-hundred three in vitro rat studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Hypertrophy in the rat model was presented in numerous articles attributed to increased protein synthesis via activation of calcium-dependent protein kinase C (PKC) isoforms, but independent from ERK activation, and may be mediated in part by endothelin-1. Phenylephrine also significantly increases nuclear muscle LIM protein (MLP) and FOXO1 expression.

Hamster in vitro

No relevant articles were identified in the literature search for this section.

Other Rodent (Guinea Pig) in vitro[864-869]

Six in vitro other rodent (guinea pig) studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Phenylephrine administration was shown to increase the action potential duration in the ventricular papillary muscle through α_1-AR activation. It also increased the delayed rectifier potassium current and prolonged the functional refractory period in the ventricle. A positive chronotropic effect

was observed, due to direct action on β-AR and indirect action due to norepinephrine release in the right atria.

Rabbit in vitro[870-874]

Five in vitro rabbit studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Phenylephrine increased atrial refractory period via α-AR and activated hypertrophic signaling via nuclear export of class II histone deacetylase and protein kinase D. Activation of β-AR by phenylephrine increased sinus node firing rate, and induced dose-related tachycardia at higher concentrations. Bradycardia was induced at lower concentrations.

Dog in vitro[875-886]

Twelve in vitro dog studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. The effect of phenylephrine on delayed afterdepolarization (DAD) provided mixed results. The amplitude of the delayed afterdepolarization induced by high calcium or ouabain in Purkinje fibers was increased by phenylephrine. However, phenylephrine demonstrated the inability to induce DAD in normal Purkinje fibers (consistently inhibiting DAD induced by isoproterenol) or ventricular cardiomyocytes. In ischemic Purkinje fibers, phenylephrine induced DAD and differentially induced triggered activity.

Action potential duration (APD) was increased at lower phenylephrine concentrations and decreased at higher concentrations.

Nonhuman Primate in vitro

No relevant articles were identified in the literature search for this section.

Human in vitro[285, 478, 763]

Three in vitro human studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Phenylephrine induced cardiomyocyte hypertrophy using HEK293 cells, increasing cell surface area, atrial natriuretic factor (ANF), and carbonic anhydrase II mRNA expression in the process.

Other Nonrodent Mammal in vitro[867, 887-891]

Six in vitro other nonrodent mammal (sheep, ferret, and cat) studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

Sheep in vitro[867, 889, 891]

Phenylephrine excited both α- and β-AR in the Purkinje fibers of sheep in 3 articles, increasing the amplitude of DAD and inducing triggered activity. In the presence of the β-blocker propranolol, the effect on DAD was biphasic. A slight excitatory effect was followed by a stronger inhibitory effect. All effects of phenylephrine were abolished by prazosin.

Ferret in vitro[887, 888]

Purkinje fibers were utilized in the studies on the ferret in 2 articles, with phenylephrine inducing early afterdepolarization (EAD) and triggered activity. These effects were shown not to depend on intracellular calcium. The action potential duration (APD) was also increased. These effects were attributed to α_1-AR stimulation.

Cat in vitro[890]

In 1 article in the cat, phenylephrine acted via α_1-AR coupled to pertussis toxin-insensitive G-protein to release IP_3-dependent intracellular NO, which in turn stimulates L-type calcium current in feline cardiomyocytes.

Nonmammal

No relevant articles were identified in the literature search for this section.

Mouse in vivo[816, 892-898]

Eight in vivo mouse studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

In the diabetic model, phenylephrine induced reflex bradycardia. Administration of phenylephrine over a 14-day period resulted in cardiac hypertrophy in non-transgenic mice and had an 80% mortality rate in transgenic mice. Administration to transgenic mice over a 7-day period resulted in severe cardiac hypertrophy, a reduction in β-AR, and an increased expression of β-AR kinase. Phenylephrine induced cardiac hypertrophy, but did not produce hypertrophy in α_{1B}-KO mice when administered over an 18-day period.

Rat in vivo[851, 899-920]

Twenty-three in vivo rat studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

Phenylephrine was shown to produce bradycardia in anesthetized rats and tachycardia in pithed rats. Baroreflex sensitivity-mediated heart rate reduction was decreased in obese

rats and SHR. Subcutaneous administration of phenylephrine limits its own rate of circulation by vasoconstrictor effects, resulting in slow onset of bradycardia. Changes in the pattern of expression, accumulation, and distribution of extracellular matrix components constitute an early event during the remodeling process associated with acute induction of cardiac hypertrophy.

Activation of α_{1A}-AR subtype induced cardiac hypertrophy, cell loss, thrombosis, and fibrosis.

Afferent information from the aortic arch and cardiopulmonary baroreceptors contributed more significantly to the reflex heart rate response to phenylephrine than did the carotid sinus baroreceptors.

Rabbit in vivo[921-927]

Seven in vivo rabbit studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

Phenylephrine administration induced reflex bradycardia. Decreases in the heart rate response were greater in obese rabbits. Repeat doses to rabbits with induced MI complicated by arrhythmias transformed ventricular extrasystole into ventricular tachycardia with an overall unfavorable prognosis.

Dog in vivo[928-941]

Fourteen in vivo dog studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

Phenylephrine administration dose-dependently induced reflex bradycardia in the dog model, and this may be part of the pressor response buffering. However, occasional positive chronotropic responses were noted. Ethanol was shown to augment the effect of phenylephrine on heart rate. Anesthesia does not appear to influence the effect of phenylephrine on heart rate, as reflex bradycardia was produced during isoflurane, enflurane, halothane, droperidol, or methoxyflurane/nitrous oxide anesthesia. Fetal injection during maternal hypovolemia produced mild bradycardia with no maternal effects observed. Phenylephrine administration did not change the transducer function of the carotid sinus baroreceptor and it neither prolonged the ventricular refractory period nor the Purkinje relative refractory period. Reflex bradycardia was induced by phenylephrine administration, even in the presence of muscarinic and ganglionic blockade. A linear relationship was noted between MAP and heart rate.

Nonhuman in vivo (Rhesus Monkey)[942]

One in vivo nonhuman primate study with other routes of administration was identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.

Phenylephrine plus lidocaine resulted in a higher level of sensory block than lidocaine alone. Phenylephrine prolonged both the duration of maximum motor block and the time for complete motor recovery, but it did not prolong the duration of maximum surgical analgesia. There were no clinically significant differences noted between phenylephrine and epinephrine when added to lidocaine solutions for spinal anesthesia.

Other nonrodent mammal in vivo

Four in vivo other nonrodent mammal studies with an IV route of administration were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters.[943-946]

Pig in vivo (nonrodent mammal)[744]

One in vivo other nonrodent mammal (pig) study with other routes of administration was identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters. Phenylephrine administration in the endotoxic shock model did not change the heart rate.

Nonmammal in vivo

Three in vivo nonmammal studies were identified as relevant for supporting the secondary phenylephrine pharmacodynamics parameters outlined in the below section.

Chicken[947]

Young embryos did not respond to high-dose phenylephrine. Older embryos responded to high-dose administration and some responded to lower doses. An increase in heart rate was not recorded for any of the embryos. The observed decrease in heart rate may be due to developing baroreceptor reflexes.

Turtle[755]

Although insignificant, reflex bradycardia was seen in the conscious turtle, but was not observed in the anesthetized turtle.

Chick[948]

Phenylephrine administration produced no significant effect on the heart rate of 5-day-old chick embryos.

4.3 Safety Pharmacology

Provided by the Sponsor:

The study by Kowey et al[666] provides cardiac safety evidence in favor of phenylephrine. Phenylephrine was administered via intravenous bolus (45 µg/kg) over 3 minutes in 5 mongrel dogs, before and after aortic arch and carotid sinus baroreceptor denervation. It was concluded that phenylephrine, through α-AR activation, exerted no direct effect on ventricular excitability or refractoriness in the normal intact dog heart.

In an amount that was the pressor equivalent to the control "arrhythmia" dose of epinephrine, phenylephrine never produced ventricular irregularities in 5 dogs under cyclopropane anesthesia. Chronotropic changes were variable, but usually the heart rate decreased by about 10 bpm. Large amounts of phenylephrine (250 µg/kg) produced occasional extrasystoles and a positive chronotropic effect in 3 dogs.[643]

Application of phenylephrine caused human ether-a-go-go-related gene (hERG) potassium channel current reduction due to a shift of the activation curve in a frog model. Application of α-1-AR antagonist prazosin, or specific inhibition of PKC or protein kinase A (PKA) abolished the phenylephrine-induced activation shift. Results suggest that cardiac repolarizing hERG potassium currents are modulated by α_{1A}-AR via PKC and PKA independent of direct channel phosphorylation.[949]

Injection of phenylephrine into the left atrium of rabbits elicited a strong increase in MAP. At the 25 µg dose, only 1 isolated arrhythmia was observed in 1 animal at the peak of hypertension.[629]

A high rate of infusion of phenylephrine frequently induced both complex and non-complex arrhythmias, but did not trigger torsades de pointes or ventricular fibrillation in pentobarbital anesthetized rabbits. Phenylephrine mildly reduced the heart rate and prolonged the QT intervals in the α-chloralose and pentobarbital groups.[927]

IV phenylephrine was used to "sensitize" anesthetized rabbits in a study of dofetilide-induced torsades de pointes. Infusion of phenylephrine increased blood pressure, reduced sinus heart rate and prolonged the QT interval equally in all animals, but in no animals did torsades de pointes or ventricular fibrillation occur before infusion of dofetilide.[924] Repeated administration of phenylephrine to rabbits with induced myocardial infarction

(MI) complicated by arrhythmias transformed ventricular extrasystole into ventricular tachycardia with an overall unfavorable prognosis.[926]

In contrast, the article by Kijtawornrat et al[665] studied the canine model in an attempt to sustain atrial fibrillation induced by rapid atrial pacing and phenylephrine. Twelve healthy male Beagles were anesthetized with morphine and maintained with α-chloralose, then infused with phenylephrine (2 µg/kg per minute). Atrial fibrillation was sustained after cessation of atrial pacing in dogs receiving phenylephrine for at least 40 minutes in 50% of the animals, but terminated within seconds in normotensive dogs.

IV infusions of phenylephrine in the dog for 30 minutes or longer caused sustained elevations in blood pressure and suppressed the depressor responses to acetylcholine (ACh) in a dose- and time-dependent manner. Steady state was reached in 30 min with a phenylephrine infusion rate of 0.3, 1, 3, or 10 µg/kg/min, but doses of 10 µg/kg/min often caused arrhythmias.[673]

In dogs under isoflurane or halothane anesthesia, a dose of 25 µg/kg per minute of phenylephrine produced a 2-fold increase in MAP within 2-3 minutes and decreased heart rate by 43%, but did not produce ventricular arrhythmias. Phenylephrine-induced arrhythmias were abolished by propranolol without a significant reduction in MAP suggesting that phenylephrine possesses some β-adrenergic effect.[686]

Only 1 out of 7 dogs survived the infusion of phenylephrine at a dose of 10 µg/kg per minute for 100 minutes. Results suggest that continuous IV infusion of vasopressors results in metabolic acidosis, cardiac failure, and irreversible shock despite the apparent initial benefits of blood pressure elevation.[671]

In the dog model, phenylephrine induced bradycardia, a group mean increase in blood pressure of 28 mmHg and caused the dynamic beat to beat relationship to increase the QT interval above baseline by ~6 ms.[699]

Phenylephrine induced or potentiated ventricular arrhythmias (VA) in 45 out of 54 dogs with inherited sudden death disorder. Arrhythmias were more severe at the higher dose of phenylephrine. Phenylephrine did not induce any VA in control dogs. The VAs increased in incidence and severity as the potency of α-stimulation was increased or unopposed by β-adrenergic activity.[933, 934] In contrast, using 19 probucol-treated dogs that serve as a model for sudden death, phenylephrine did not induce ventricular fibrillation (VF) in any of the 19 dogs. Nine out of 11 dogs administered a mixture of isoproterenol and phenylephrine developed VF.[930]

In a study by Frederick et al,[950] within minutes to hours of IV administration of phenylephrine in horses, all 5 horses developed severe hemothorax, hemoabdomen, or both. Four of the 5 died of hemorrhagic shock, and 1 survived after receiving a blood transfusion.

A study by Murphy and Johanson[575] examined the permeability of the blood-brain barrier (BBB) by nonelectrolyte and protein tracers in Sprague-Dawley rats. As intravenous phenylephrine elevated BP, it increased the permeation of tracers into the BBB, an attribute of protective vasoconstriction associated with α-agonist activity. The augmented permeation of nonelectrolyte tracers during acute hypertension occurred predominantly by diffusion rather than vesicular transport. If the agent-induced rise in BP was blocked, no change in tracer permeation was observed. The study by Johnston et al[702] determined phenylephrine did not cause cerebral vasoconstriction after rewarming from hypothermic CPB in the dog, suggesting the BBB was preserved during bypass.

The review article by Talegaonkar and Mishra[951] indicates the key to being able to bypass the BBB is through intranasal delivery due to the unique connection between the brain and the nose. This would offer distinct advantages over delivery across the BBB or direct delivery to the brain. The intranasal method would allow for rapid, non-invasive delivery, reduced systemic exposure and side effects by bypassing the BBB, would not require modification of the therapeutic agent, it works for a wide range of drugs, and allows increased bioavailability by avoiding first-pass elimination.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

It is known that phenylephrine, when given orally, is metabolized by the monoamine oxidase type A (MAO-A) system, undergoes extensive first-pass metabolism, and is highly bound to plasma proteins. The established half-life in humans is 2.1 to 3.4 hours.[3]

5.2 Toxicokinetics

See below

6 General Toxicology

Overview of Toxicology studies done by NTP; Reviewer's Comments:

2-week mouse (negative)
12-week rat repeat-dose tox. study (dietary)
Mortality: 4/10 males receiving the highest conc. (20,000 ppm) died, 2/10 males died at 10,000 ppm and 1/10 male at 5,000 ppm. (1 ppm= 1mg/kg)
Body weight: Decrease in all groups except lowest dose female group.
Feed consumption was lower in all groups.
Rats were hyperexcitable in all but lowest dose groups.
Organ weights: Absolute adrenal and heart weights were lower in both sexes at the highest dose. Relative adrenal and heart weights were lower in the highest dose in both sexes.
Opthalmology: Chronic keratitis of the eye was observed in 4/8 males and 8/10 females at the highest dose and 4/8 males and 6/10 females at the middle dose.
Histopathology: Minimal to mild testicular atrophy was observed in 4/8 males at the highest dose and 5/6 males exhibited seminal vesicle atrophy at the highest dose. Mild to moderate ovarian atrophy was observed in 5/10 females that received the highest dose.

7 Genetic Toxicology

Performed by NTP:
Ames (negative with and w/o metabolic activation))
Mouse lymphoma (equivocal at toxic doses)
CHO (chromosome aberration negative but induced sister chromatid exchanges w/o metabolic activation)
Rat micronucleus negative

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

Performed by NTP:
2-year mouse and rat carcinogenicity studies were negative

9 Reproductive and Developmental Toxicology

From the literature:

Reproductive Toxicology Studies: Seg. II studies: Rabbit fetal growth retardation and onset of early labor when given in last trimester [Shabanah, et al., Effect of epinephrine on fetal growth and the length of gestation. Surg. Gynecol. Obstet. (1969) 341-343].

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

1) Phenylephrine was shown not to produce arrhythmias in the rabbit and showed no direct effect on ventricular excitability or refractoriness in the dog
2) Large doses of PE can produce occasional extrasystoles and QT prolongation
3) PE does not produce torsades de pointes.
4) Of the 624 articles presenting the vasoconstriction/pressor action of PE, it effectively constricted blood vessels and/or raised blood pressure in 619 articles (99.2%).
5) PE has been shown to be neither mutagenic nor carcinogenic.
6) Preliminary results of the canine pharmacology study confirmed that IV PE increases blood pressure in a canine model of endotoxic shock. PK of PE in dog closely mirrors PK in humans.

12 Appendix/Attachments

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