Clinical and experimental studies on theophylline toxicity: in search for and antidote

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Methylxanthines

- Methylxanthines have been effectively used therapeutically in respiratory disorders, e.g. COPD, asthma, cor pulmonale, apnea in newborns, etc.

- Caffeine (Tea/Coffee) and theophylline (as a drug) commonly used

- Theophylline, a methylxanthine bronchodilator, given for asthma and COPD, and newer uses emerging

- Steroids are the first line of drugs for asthma but are given along with bronchodilators like theophylline to reduce their dosage and reverse steroid resistance

- Theophylline is an effective, pharmacoeconomically viable drug, but has a narrow therapeutic index, i.e. low margin of safety

Theophylline…

- Toxicity profile includes cardiotoxicity, GI toxicity and CNS toxicity
- Susceptibility to cardiac arrhythmias and seizures is particularly increased in asthmatics in extremes of age
- Cardiac arrhythmias and seizures not preceded by milder warning symptoms and conventional anti consultants are only partially effective against these seizures
- However, in view of its recently demonstrated anti-inflammatory and immunomodulatory effects, it is re-emerging as an important adjunct to therapy in asthma and COPD
- Strategies are being devised to improve the safety profile

Theophylline……

- Adenosine antagonism and PDE inhibition are commonly proposed mechanisms of action of theophylline
- CV effects due to increased vascular tone, myocardial contractility, conduction and sympathetic nervous system
- A combination of hemodynamic and neurohumoral effects
- Chronic methylxanthine intake increases CNS and cardiac risk factors
- Mechanisms of such toxicity poorly understood

PHARMACOVIGILANCE

- The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems

- A tool for drug safety

- Primarily a regulatory issue, but data/concept may to extended to device pharmacological strategies for rational therapy

ADR monitoring in Asthma and COPD

- 120 patients of bronchial asthma and COPD were selected from the VPCI OPD
- Ethical clearance and GCP guidelines
- Standard inclusion/exclusion criteria
- Diagnosed by clinical features and PFT findings
- ADR profile was recorded as per Pharmacovigilance Programme of India proforma
- Dechallenge and rechallenge were done wherever appropriate
- Causality Assessment was done by using the Naranjo`s scale

ADR profile with drugs in asthma and COPD

Drugs	**Br. Asthma**	**COPD**	**Profile**
Inhaled steroids	54/60 (90%)	30/60 (50%)	Sore throat,dysguesia,hoarseness,gloss-itis, others
Inhaled anticholinergics	25/40 (62%)	10/44 (23%)	Dry mouth,thirst, urinary difficulty
Inhaled beta-2 agonists	25/60 (43%)	3/60 (5%)	Hand tremors, palpitations
Oral steroids	28/32 (87%)	3/14 (21%)	Wt. gain, acne, cramps, mood changes
Oral theophylline	14/20 (70%)	20/43 (46%)	Anxiety, dyspepsia, ms spasm, paresthesia, etc

ADR monitoring in OAD…

- Sex distribution of patients were equal in asthma whereas COPD patients were predominantly males
- All patients received multi-drug treatment schedules (inhalation and oral)
- Most patients received inhaled steroids and bronchodilators
- Few received mucolytics, antibiotics, analgesics, etc.

Prescription monitoring in obstructive airway disease (theophylline)

Prescriptions	**Total No.**	**With theophylline**	**%**
All patients	120	63	52.6
Br. Asthma	60	20	33.3
COPD	60	43	71.6

ADR incidence with theophylline

Patients	Received Theophylline	Showed ADRs	%
Br. Asthma	20	14	70
COPD	43	20	46.5
Total	63	34	53.9

Incidence of ADRs with theophylline in asthma and COPD

ADR	Asthma	COPD
Dyspepsia	45%	65%
Anxiety/Palpitation	**50%**	**60%**
Spasm of Muscles	35%	30%
Insomnia	40%	10%
Dizziness	15%	10%
Theophylline Withdrawal Induced Constipation	-	5%
Paraesthesia	20%	10%
Others	10%	5%

CASUALITY ASSESSMENT OF ADRs DUE TO ORAL THEOPHYLLINE USING THE NARANJO'S SCALE

Drug	**Highly Probable (9)**	**Probable (5-8)**	**Possible (1-4)**	**Doubtful (0)**
Oral Theophylline	Muscle spasm of calves (most commonly) sternocleido-mastoid, intercostal muscles	(1)Dyspepsia (2)Insomnia (3) Anxiety & Palpitation (4)Dizziness (5)Withdrawal induced Constipation (6)Paraesthesia (7)Colicky Pain (8)Diuresis		

Summary

- Most ADRs were mild to moderate in nature and tolerable
- Few, particularly those related to oral steroids and theophylline, were intolerable and required dose reduction
- Causality assessment showed that most were in the probable category (score from 5 - 8)
- Some effects of oral theophylline and steroids were having scores > 9 (highly probable)
- Such focused studies are helpful in reducing ADRs in OAD and rationalizing drug therapy

Reverse Pharmacology

- Experimental evaluation/documentation of clinically observed findings
- Reverse pharmacology is an alternative strategy for new drug development
- Reverse pharmacology can play an important role in safety pharmacology studies
- A practice which was successfully employed in the past (eg. Reserpine) and is being more scientifically implemented now

Reverse pharmacology studies: Basis

- The role of oxidant/anti-oxidant balance in obstructive airway disease has been proposed
- Oxidative stress and drug toxicity connection: adriamycin, paracetamol, etc.
- A connection between theophylline and oxidative stress: OFRs formed during xanthine-XO interactions
- Earlier studies showed that theophylline induced seizures were attenuated by antioxidants
- Preclinical study planned to evaluate the MOA of Theophylline induced ADRs viz. anxiety and tachycardia

Effects of anti-oxidants on Aminophylline induced Anxiety

Treatment (mg/kg)	Elevated Plus Maze (%)	
	OA entry	OA time
Vehicle	30.0 ± 5.6	23.2 ± 3.6
Amino (50)	16.6 ± 4.2*	13.3 ± 2.8*
Amino (100)	9.0 ± 1.3*	5.3 ± 1.1*
TP(40)+Amino(100)	22.2 ± 7.0	15.2 ± 5.0
Mel(50)+ Amino(100)	18.7 ± 6.5[a]	12.1 ± 4.6 [a]

n=8/ group ; TP: tocopherol; Mel: melatonin

* $p < 0.05$ (compared to vehicle)

[a]. $p<0.05$(compared to Amino-50)

Aminophylline (A) induced anxiety and oxidative stress markers

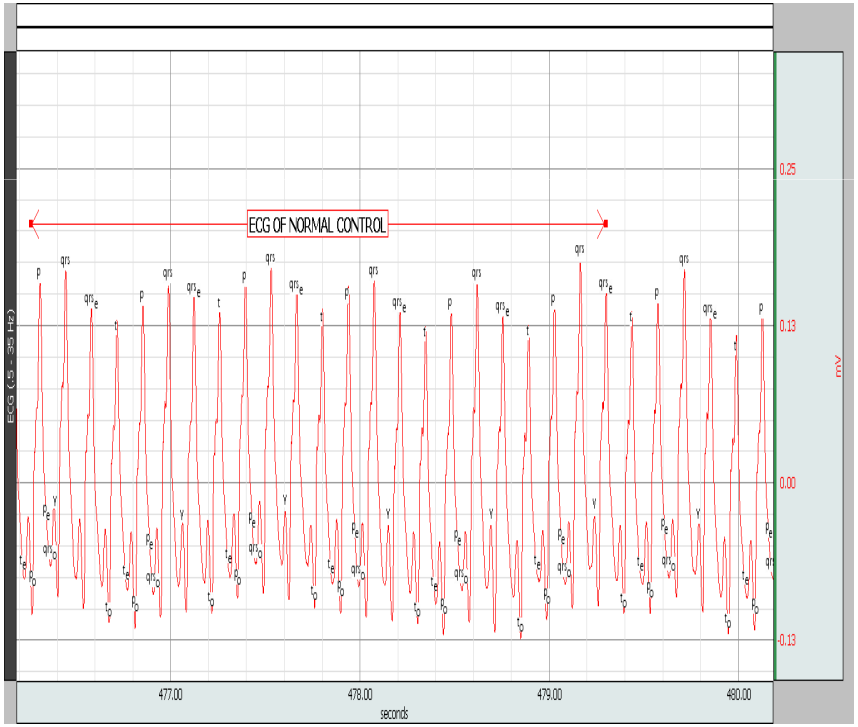
Treatment (mg/kg)	**EPM (%OAE)**	**Brain MDA nmol/mg pr.**	**Brain GSH μmol/g tissue**
Controls	23.6 ± 3.1	5.2 ± 0.5	9.8 ± 0.3
A (100)	9.0 ± 1.3 *	8.2 ± 1.2 *	6.7 ± 0.8 *
A (50)+ RS	4.0 ± 1.2 *	7.6 ± 0.4 *	4.9 ± 0.4 *
TP + A (100)	17.1 ± 4.4	5.0 ± 0.2	8.0 ± 0.3
Mel + A (100)	22.6 ± 3.8	4.2 ± 0.5	7.6 ± 0.5

Effects of aminophylline on Mean B.P and Heart rate

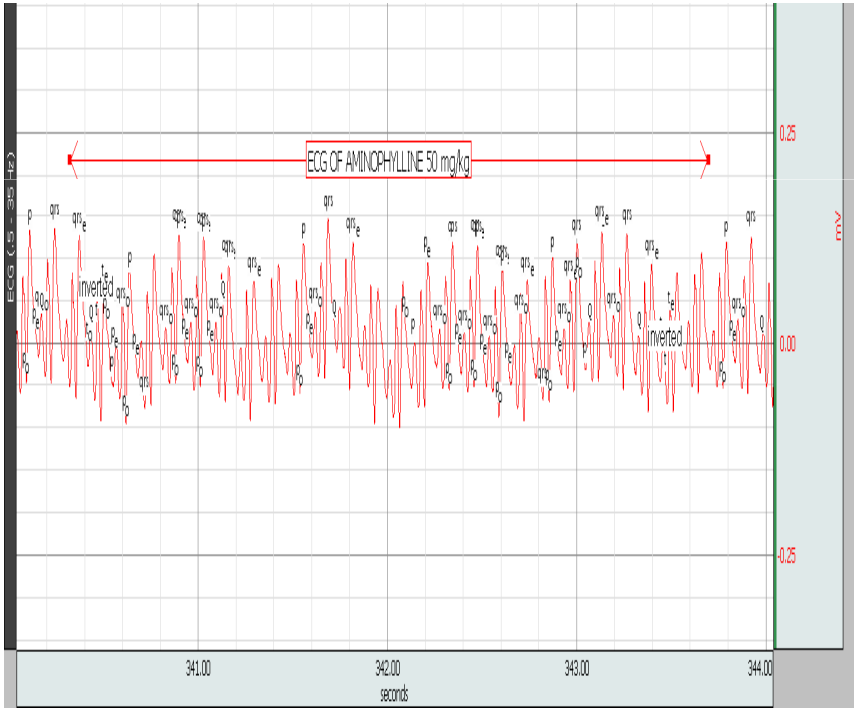
Treatment (mg/kg)	Mean B.P(mm Hg)	Heart rate(BPM)
Controls	70.96 ± 2.30	413.79 ± 5.60
Aminophylline (50)	81.00 ± 6.45	402.90 ± 8.52
Aminophylline (100)	80.18 ± 3.33	480.00 ± 6.15 *
Aminophylline (150)	91.66 ± 7.20 *	531.00 ± 16.66 *

ECG TRACING BY BIOPAC SYSTEM

CONTROL

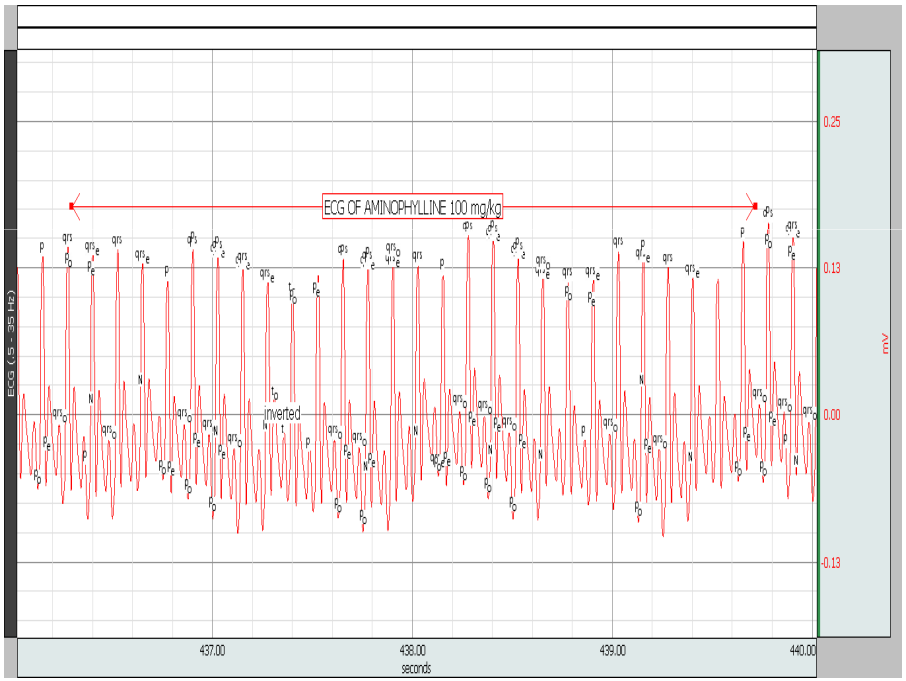


AMINO-50

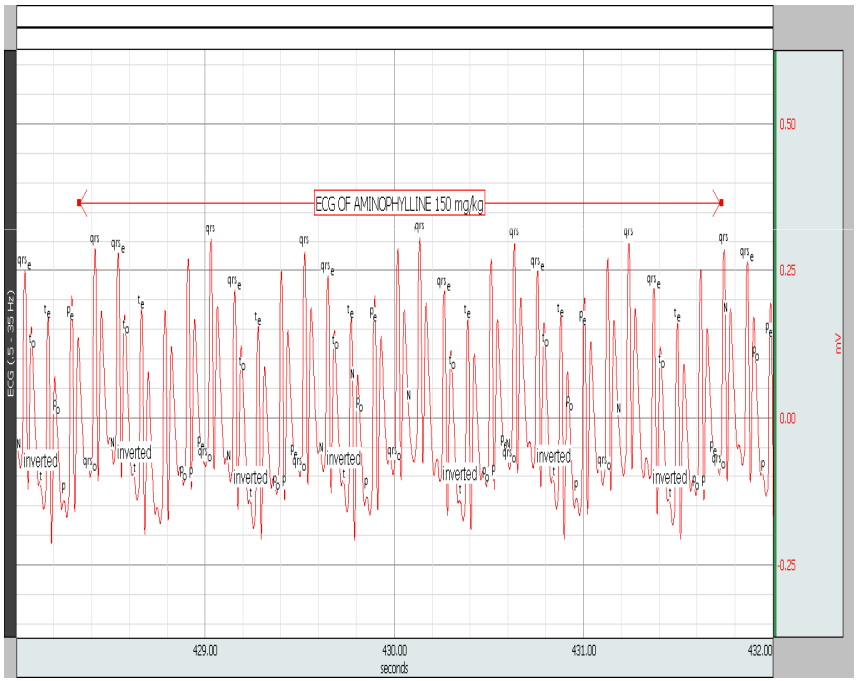


ECG TRACING BY BIOPAC SYSTEM

AMINO (100 mg/kg)



AMINO(150mg/kg)

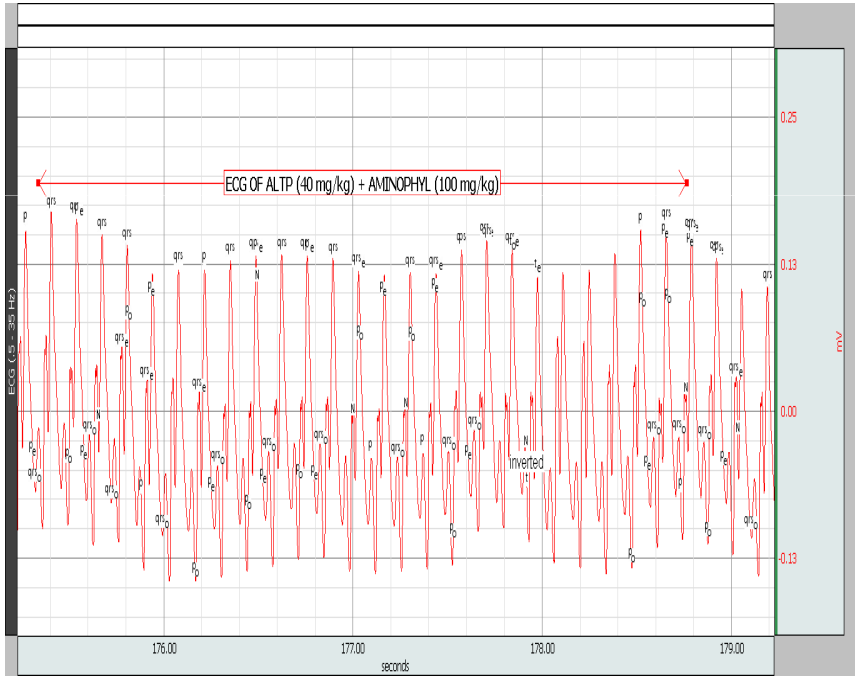


Effects of tocopherol on aminophylline induced cardiotoxicity

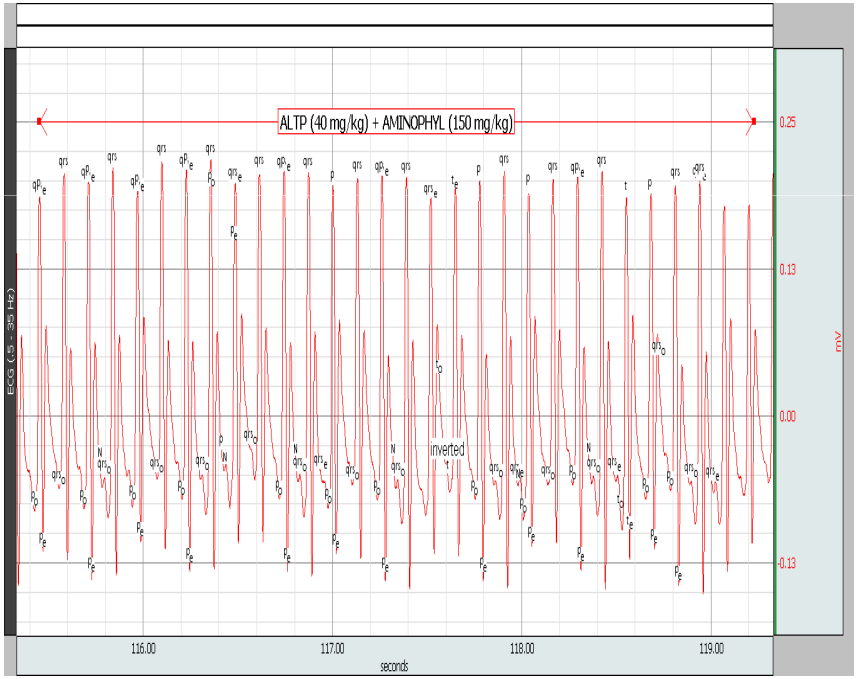
Treatment(mg/kg)	Mean B.P	Heart rate
Control	70.96 ± 2.30	413.79 ± 5.60
Amino (150)	91.66 ± 7.20	531.00 ± 16.66 *
α-tocopherol (20) + Amino(150)	91.80 ± 6.96	529.40 ± 19.18
α-tocopherol (40) + Amino(150)	72.62 ± 11.49	405.88 ± 29.37 [a]

Antioxidants and aminophylline toxicity

α-TP (40 mg/kg) + AMINO (100 mg/kg)



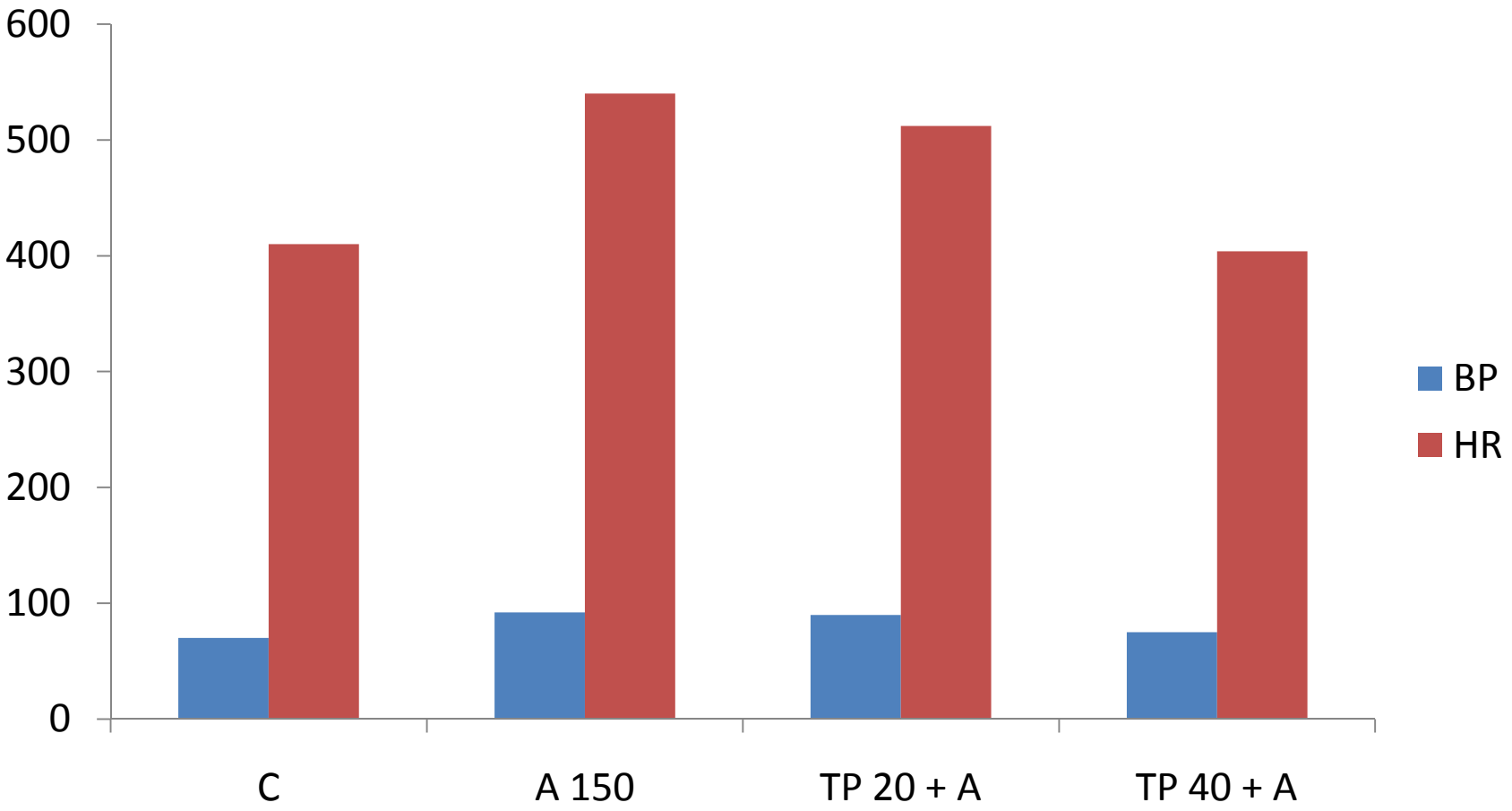
α-TP (40 mg/kg) + AMINO (150 mg/kg)



Effects of Aminophylline on oxidative stress markers

Group	MDA (nmol /mg protein)	GSH (µmol/mg protein)	SOD (U/mg protein)
Controls	0.35 ± 0.06	0.57 ± 0.03	0.51 ± 0.15
Aminophylline (50 mg/kg)	0.42 ± 0.10	0.54 ± 0.09	0.60 ± 0.21
Aminophylline (100mg/kg)	0.66 ± 0.08 *	0.44 ± 0.06	0. 44 ± 0.40
Aminophylline (150mg/kg)	1.02 ± 0.18 *	0.40 ± 0.07 *	0.30 ± 0.02 *

Effects of α-tocopherol (TP) on aminophylline (A) induced cardiotoxicity



Summary and Conclusion

- These experimental studies show that theophylline-induced anxiety and tachycardia may be due to oxidative stress, and antioxidants may have protective role

- Thus it could be speculated that treatment with antioxidants may be helpful in preventing such ADRs due to theophylline

- The data of clinical and preclinical studies show that such translational approach could help to highlight some yet unexplored areas of safety pharmacology and toxicology

- The deliverable could be rationalization of drug therapy

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Thank You