Pharmacy Friday

Brief pearls related to acute care pharmacology and evidence-based medicine
Other pearls found at:

- https://sites.google.com/presby.edu/pharmacy-friday

Drug Induced Hyperthermia (DIH)

Introduction

1. Temperature is regulated by the hypothalamus-pituitary-adrenal axis; therefore, any drugs that disrupt neurotransmitters such as norepinephrine, serotonin and dopamine can potentially cause DIH.
2. Hyperthermia vs Fever: Temperature ≥ 38.2° C
   a. **Fever:** regulated by hypothalamus; Antipyretics effective
   b. **Hyperthermia:** not regulated by hypothalamus; Antipyretics ineffective
3. It is important to rule out other potential causes of hyperthermia (e.g. thyrotoxicosis, CNS infection and pheochromocytoma)

Types of Hyperthermia

Type of DIH	Neuroleptic Malignant Syndrome	Serotonin Syndrome	Anticholinergic Syndrome	Sympathomimetic Syndrome	Malignant Hyperthermia Syndrome
Causative Agent	Antipsychotics (e.g. haloperidol; associate with higher doses), metoclopramide, promethazine, Abrupt DC of levodopa	SSRIs (e.g. fluoxetine, citalopram), TCAs (e.g. amitriptyline), MOAI, Linezolid, MDMA, tramadol, St. Johns Wort	Antihistamines, anticholinergics, TCAs, belladonna, antispasmodics (e.g. oxybutynin), mushrooms,	Ecstasy, cocaine, MOA Inhibitors	Succinylcholine, volatile anesthetic gases
Mechanism	Poorly understood; Hypothalamus Dopamine depletion/blockade	↓ reuptake of 5HT → ↑ 5HT	Muscarinic blockade → impairs sweat gland function →	↑ 5HT / NE / Dopamine → ↑ metabolism and ↓heat displacement	Mutation of RYR-1 → ↑ sarcoplasmic Ca → muscle contraction
Clinical Presentation	Extrapyramidal rigidity, ↑CK, diaphoresis, AMS, abnormal BP, ↑HR	Hyperreflexia, AMS, rigidity, ↑HR, myoclonus, clonus,	Dry mouth, mydriasis, ↑HR, flushed, AMS, urinary retention	AMS, seizures, coagulopathy, myocardial dysfunction	↑HR, ↑RR, muscle rigidity, metabolic acidosis, HyperK
Onset	Gradual: days - years	Rapid: mins - hours	Rapid: hours - days	Rapid: hours - days	Rapid: mins - hours
Treatment	- DC offending agent - Fluids - BZD for rigidity - **Mod**: Bromocriptine; Less evidence for levodopa or amantadine - **Severe**: Dantrolene + Bromocriptine +/- amantadine	- DC offending agent - External cooling - BZD for rigidity - Supportive Care - Mild-Mod: Cyproheptadine - Not Recommended: propranolol, dantrolene, bromocriptine	- DC offending agent - External cooling - BZD for rigidity - Physostigmine	- DC offending agent - External cooling - Supportive Care - BZD / Barbiturates for rigidity	- DC offending agent - Hot Line: 1-800-644-9737 - Hyperventilate w/ 100% O2 - Dantrolene IV Push - Continue sedation with opioids / propofol - External cooling - Treat HyperK if present

SSRI - Serotonin reuptake inhibitor; TCA - tricyclic antidepressants; MOAI - Monoamine oxidase inhibitors; CK - creatinine kinase, BZD Benzodiazepine

Pharmacology

Drug	Dantrolene	Bromocriptine	Physostigmine	Cyproheptadine
Dose	**MH** Bolus: 2.5 mg/kg IV push Repeat 1mg/kg until decrease in $ETCO_2$ and muscle rigidity Maintenance: 1 mg/kg Q6H **NMS** Bolus: 1-2.5 mg/kg IV	2.5 mg Q8H PO; Increase dose to achieve effect; Max 45mg/day	Adult: 0.5 - 1 mg Q10 minutes (Max 2mg in 1st Hour) Ped: 0.02 mg/kg, Max 0.5mg per dose Q10 minutes	Initial: 12mg PO x 1, then 2mg Q2H until symptoms stop Maintenance: 8mg Q6H

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	Maintenance: 1 mg/kg Q6H for 24Hr then change to PO Max: 10 mg/kg/day			
MOA	Ryanodine receptor 1 antagonist → inhibit sarcoplasmic calcium release → relax skeletal muscles	Dopamine agonist → ↑ Dopamine in hypothalamus	acetylcholinesterase inhibitor	antagonist of 5HT1/2A
Formulation	IV (Ryanodex - dilute 250mg with 5mL SWFI) / PO	PO	IM / IV	PO
PK/PD	Onset: 1 minute Half-life: 4-11 hours	Onset: Half-life: ~6hrs	Onset: 3-8 minutes Duration: 45-60 minutes Half-life: 1-2 hours	Onset: 6 hrs Half-life: ~16 hrs
Adverse Effects	Muscle weakness, flushing, drowsiness; hepatotoxicity	Hypotension, psychosis, N/V	Bradycardia, seizures, cholinergic effects (SLUD)	Sedation

Overview of Evidence

Author, year	Design/ sample size / Disease State	Intervention & Comparison	Outcome
Reulbach 2007	Case Series N = 271 **NMS**	1. Dantrolene monotherapy 2. Dantrolene + other medication 3. Other medication 4. Only supportive measures (cooling, fluids, correcting electrolytes)	- Dantrolene monotherapy and other medication (bromocriptine, amantadine or electroconvulsive therapy) had similar effectiveness within 24 hours. - Complete remission days was ~ 9 days except dantrolene with additive medication which was 19 days. - Dantrolene monotherapy had ↑ mortality - Time to treatment not reported and dantrolene
Burns et. al 2000	Retrospective observational/ N=52 **Anticholinergic Syndrome**	Physostigmine vs Benzodiazepines (BDZ)	- Physostigmine ↓ agitation and reversed delirium significantly better than BDZ. - BDZ ↓ agitation but did not reverse delirium - Physostigmine ↓ complications and recovery.
Arens et. al 2017	Retrospective observational/ N=191 **Anticholinergic Syndrome**	Physostigmine	- 73% of patients had improvement or resolution of delirium with only initial dose of physostigmine & 36% of patients received additional doses of physostigmine. - Non-diphenhydramine antihistamine exposure had 100% response to physostigmine & anticholingergic plants exposure or combination products had partial response to physostigmine.
Nguyen et. al 2019	Case Series N=288 **Serotonin Syndrome**	Cyproheptadine Vs. No Cyproheptadine	- No difference between patients that received cyproheptadine and no cyproheptadine. - No difference in severe outcomes between cyproheptadine and no cyproheptadine. - Patients that received cyproheptadine were significantly older, intubated, sedated and admitted to critical care unit.

Conclusions

1. Get an accurate medication history
2. Rule out other causes
3. **Stop the offending agent**. If MH start hyperventilation to flush volatile gases and give dantrolene.
4. Supportive care is the most common treatment

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References

1. Reulbach U, et al. Crit Care. 2007;11(1):R4.
2. Burns MJ, et al. Ann Emerg Med. 2000 Apr;35(4):374-81.
3. Nguyen H, et al. J Clin Pharm Ther. 2019;44:327–334.
4. Arens AM, et al. Clin Toxicol (Phila). 2018 Feb;56(2):101-107.
5. Jamshidi N, et al. Aust Prescr 2019;42:24–8.
6. Musselman ME, et al. Am J Health Syst Pharm. 2013 Jan 1;70(1):34-42.
6. Dantrolene. Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved October 10, 2018, from http://www.micromedexsolutions.com/
7. Cyproheptadine. Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved October 10, 2018, from http://www.micromedexsolutions.com/
8. Bromocriptine. Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved October 10, 2018, from http://www.micromedexsolutions.com/
9. Physostigmine. Micromedex [Electronic version].Greenwood Village, CO: Truven Health Analytics. Retrieved October 10, 2018, from http://www.micromedexsolutions.com/

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