Dipyrrone / Metamizole - Update

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Disclosure

TEVA Israel has supported the conference

BUT NOT FOR THIS PRESENTATION
Overview

• Background
• Safety
• Efficacy
• Use during pregnancy
• Use during lactation
Dipyrone (Metamizole) – Background

• Metamizole was first marketed in Germany in 1922

• Pharmacological category - NSAID’s- weak NSAID (pyrazolone family)

• Has analgesic and antipyretic properties

• Effective against post –operative pain (The Cochrane collaboration 2011)

• Has an anti-spasmolytic property.

• The drug is registered in Israel for adults and children from 3 month of age.
Mechanism of action

• Inhibition of a central COX-3 and activation of the opioidergic system and cannabinoid system

• More than 50% binds onto plasmatic proteins: short plasmatic half-life (I.V. 14 minutes)

• Elimination – mostly renal.
Countries that have Dipyrone on market

Austria  Latvia  Pakistan  Brazil
Belgium  Lithuania  China  Argentina
Spain  Czech republic  Vietnam  Uruguay
Germany  Bulgaria  Israel  Paraguay
Switzerland  Hungary  Egypt  Colombia
Nederland  Slovenia  Indonesia  Peru
Italy  Russian federation  Venezuela  Mexico
Greece
Portugal
Countries where Metamizole is not approved

- **Sweden**: banned dyirone in 1974, reintroduced metamizole in 1995, withdrew it again in 1999
- **USA**: Not FDA approved- withdrew dipyrone 1977
- **Canada**
- **UK**
- **Australia**: withdrew metamizole in 1964
- **Norway**
- **Finland**
- **New Zealand**
- **Denmark**
- **Singapore**: withdrew metamizole 1978
Adverse reactions:

• Agranulocytosis:
  
  I. Rarely been reported
  
  II. Idiosyncratic, unpredictable

• Allergic (rare): Anaphylactic shock

• Other Hematological ADR’s: anemia, leucopenia and thrombocytopenia.
USA (1964)

- **1955-1959**: (US Registry) 10 Cases of leucopenia associated with dipyrone. (None of the patients were children)
- **Since 1960** - 18 cases (7 of the patients were children)
- 9 cases – reported from a foreign countries
- 14 cases – reported from foreign literature
- **37% (19 patients) of the patients died**
- Some of the cases reported a **cross reactivity** between aminopyrine and dipyrone.

Dipyrone and aminopyrine are so similar that there is no reason to suspect that they are not equally likely to produce agranulocytosis.

JAMA 1964 Sep 21;189:938-41.

Agranulocytosis induced by dipyrone, a hazardous antipyretic and analgesic.
Huguley CM Jr.
Sweden (SADRAC) 2002

• Cases of agranulocytosis submitted to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) 1996-1999 were identified.

• 3567 case records were investigated at 10 hospital departments as well as stored prescriptions at six pharmacies during a 3-month study period.

Results:

• Ten cases of agranulocytosis during treatment with metamizole have been reported to SADRAC over the period 1996 to 1999.
• During the 3-month study period metamizole was prescribed to 666 (19%) inpatients.


Utilization pattern of metamizole in northern Sweden and risk estimates of agranulocytosis.
Sweden

- Of these, approximately 96% received dipyrone for less than 1 week, 7.2% had used the drug previously.
- 112 metamizole prescriptions for outpatients were found at the participating pharmacies.
- The SADRAC assumed that the calculated risk of agranulocytosis would be approximately 1 out of every 31,000 metamizole-treated inpatients and one of every 1400 metamizole-treated outpatients.

Utilization pattern of metamizole in northern Sweden and risk estimates of agranulocytosis.
Metamizole (dipyrone)-induced agranulocytosis: Does the risk vary according to ethnicity?

J. Clin Pharm Ther 2019

• Based on spontaneous reports from Spain, British, Irish and Scandinavians are in greater risk of dipyrone induced agranulocytosis.
• At least 4 drugs has been associated with variant HLA alleles.
• Preliminary evidence also suggests that the presence of specific variant HLA alleles may sensitized individuals to dipyrone induced agranulocytosis.
On 2012, three cases of neutropenia were reported from MEIR medical center to the MOH, possibly due to dipyrone use.

A committee was established.

After careful examination – the 3 cases were not related to dipyrone use.

Agranulocytosis in the 3 cases was attributed to other medications: Valproic acid, carbamazepine.
A survey – directed to the MOH (2012)

• Application to all emergency departments in ISRAEL, looking for cases of drug-induced agranulocytosis not related to chemotherapy
• 19 hospitals were included in the report.
• 100 cases of agranulocytosis /neutropenia were reported to the MOH.
• Only 3 of them were possibly related to dipyrone.
• Rambam Medical Center- 1 million doses of dipyrone each year- no case of agranulocytosis
The committee discussed two possible actions:

1. Black Box in the leaflet of the drug
2. To change the status of dipyrone to a prescription drug

Both decisions were rejected.
Withdrawal of dipyrrone from the market

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<th>PRO</th>
<th>CONS</th>
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<td>Idiosyncratic <strong>RARE</strong> adverse drug reaction such as: Anaphylaxis Agranulocytosis Pancytopenia Anemia Interstitial nephritis (<strong>in case of overdose</strong>)</td>
<td>The use of NSAID’S will rise; • Patients with renal impairment can’t use them. • Patients that treated with meds which are incompatible with NSAID’S can’t use them. • Most of the elderly patients already have renal impairment – cannot use them. The use of opioids will increase. The use of illicit drugs may increase. (Marijuana)</td>
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Analgesic Properties – Evidence Based efficacy

• 9 studies were found

• Dose range of dipyrone: 500mg-2.5 gr.

• Several routs of administration were used (IV, IM, oral, rectal suppositories)

Cochrane collaboration 2011
Analgesic Properties – Evidence Based Efficacy

• All studies had a control groups in which other drugs has been used: Ibuprofen, paracetamol, aspirin, ketoprofen, ketorolac, tramadol, petidine, flurbiprofen, dexibuprofen, suprofen.

• Placebo was included in the 8 of these studies.

Cochrane collaboration 2011
Analgesic Properties – Evidence Based efficacy

Results:

- 70% of the patients experienced 50% reduction of pain, at least 4-6 hours after oral administrations of 500mg dipyrone compared to 30% of placebo patients.
- The necessity of additional analgesic treatment was in 7% of the patients who were treated with dipyrone compared to 34% of the placebo patients who were in need for additional analgesic.
- No significant adverse drug reaction were reported

Cochrane collaboration 2011
Analgesic Properties – Evidence Based efficacy

• Metamizole is the most frequently used (scheduled) analgesic in German nursing homes with a large proportion receiving this analgesic as long-term therapy.

• 852 residents from 21 nursing homes were included.

• They were on average 83.5 years old.

• The most frequently prescribed substances were metamizole (40.6%) and paracetamol (35.6%).

• Metamizole prescribing increased with decreasing renal function (37.3%; 40.9% and 50.9% for eCCR ≥ 60; 30–59 and <30 ml/minute).

Pain medication in German nursing homes: a whole lot of metamizole.
Analgesic Properties – Evidence Based Efficacy

• The proportion of residents receiving metamizole increased with age (up to 47.4% in persons aged 90 years and over).

• 66.9% received metamizole for at least 90 days and 23.2% for at least 365 days (mean duration 276 days)

• The dominating role of metamizole might reflect a perceived lack of alternatives in this population.

• No adverse drug reactions were reported in this study.

Severe Headache Treatment with dipyrone efficacy

- 4 studies were found with 636 patients.
- One of the studies examined two dosages 500mg, 1 gr.
- Both dosages were significantly effective compared to placebo in severe headache.

Cochrane database 2007
Severe headache treatment with dipyrone: efficacy

• 1 gr of dipyrone was significantly effective compared to 1 gr of aspirin.

• No significant ADR’S were reported.

• The conclusion: dipyrone was effective in treatment of migraine and headaches.

Cochrane database 2007
Anti pyretic properties
efficacy

- 628 febrile children divided in three groups of Ibuprofen, paracetamol, dipyrone
- Children age range: 6 months - 6 years
- The drugs decreased temperature in 555 patients who have completed the study.

Anti pyretic properties

Temperature normalization rates in the ibuprofen and dipyrone groups (78% and 82%, respectively) were significantly higher than the acetaminophen group (68%, P=0.004).

After 4-6 hours, mean temperature in the dipyrone group was significantly lower than the other groups.

All three drugs showed comparable tolerability profiles.

Anti pyretic properties efficacy

- 75 children were randomly assigned to receive a single dose of oral ibuprofen (10 mg/kg), oral dipyrone (15 mg/kg) or IM dipyrone (15 mg/kg).
- Children age range: 6 months-6 years with fever
- The primary outcome: mean temperature reduction after 30, 45, 60, 90 and 120 minutes.
- Secondary outcomes were fever-associated symptoms and clinical adverse events.
- Antipyretic efficacy and tolerability of oral dipyrone and intramuscular dipyrone were similar for oral ibuprofen.

Pharmacovigilance Risk Assessment Committee (PRAC). December 2018 (pregnancy)

- No evidence of teratogenic or embryo toxic effects of metamizole when used during the 1st trimester.
- The data on metamizole during pregnancy and breastfeeding are scarce.
- There is evidence of fetotoxicity when used in the 3rd trimester. (fetal renal impairment & ductus arteriosus constriction)
- An association with acute lymphocytic leukemia & Wilms tumor in infants up to 2 years of age is unlikely but data are insufficient to completely rule out such a risk
Pharmacovigilance Risk Assessment Committee (PRAC) (pregnancy)

• Single doses of metamizole during the 1st and 2nd trimester are acceptable in selected cases where paracetamol, ibuprofen or diclofenac are not an option.

• Metamizole should not be used during the 3rd trimester.

• In cases of repeated use during the 3rd trimester
  I. Amniotic fluid
  II. Ductus arteriosus

  Should be controlled by ultrasound and echocardiography.
Pharmacovigilance Risk Assessment Committee (PRAC). (Breastfeeding)

• Metamizole should not be used during breastfeeding due to possibility of high relative infant dose and the overall evidence is scarce.

• Very low number of reported serious adverse drug events in pregnancy and lactation over several decades suggest a low overall risk in case of inadvertent or indispensable short term use of metamizole during pregnancy and lactation

• Other Better-investigated analgesics should be preferred.
Dipyrone safety during pregnancy

• 108 women who used metamizole during the first trimester of pregnancy were recruited from 4 teratogen information centers in Israel and in Italy
• The study group was paired for age, smoking habits and alcohol consumption with a comparative group exposed to acetaminophen
• Maternal demographics and medical history, birth weight, gestational age at delivery, rate of live births, spontaneous abortions and fetal distress were comparable in both groups

European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 119, Issue 2, 1 April 2005, Pages 176-179
Dipyrrone safety during pregnancy

The rate of major malformations in the metamizole group (3%) did not differ significantly from the rate in the comparative group (2%) ($P = 0.57$, relative risk = 1.55, 95% confidence interval 0.26–9.05).

**Conclusions:**
The exposure to metamizole during the first trimester of pregnancy is probably not associated with a significantly increased risk for malformations or spontaneous abortions.

*European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 119, Issue 2, 1 April 2005, Pages 176-179*
Dipyrrone – postpartum pain

• Treatment protocols were received from 26 maternity departments.
• All use oral paracetamol alone or combined with another drug.
• Dipyrrone is used in 22/26 departments, despite the fact that this medication is not approved for use during Lactation.

Harefuah. 2009 Jul; 148(7): 427-431, 477, 476
Conclusions:

Since the secretion in to the breast milk of dipyrone is negligible (1.2%) there is no contraindication to use it in lactating women.

Israeli teratology centers forum statement pregnancy

• Dipyrrone is allowed at therapeutic doses up to 28\textsuperscript{th} week of pregnancy
• The dose of dipyrrone after 28th week of pregnancy should not be exceeded up to 3 g / day
• Repeated doses should be avoided.
• In case of severe continuous pain – Tramadol or Codeine may be suggested.
Due to low relative infant dose and low excretion to the breast milk.

- Dipyrrone is allowed during breastfeeding in a regular dosage up to 4 gr /day.
In conclusion

• Dipyrrone was proved to be effective as analgesic and antipyretic agent.

• The medication is safe during pregnancy and lactation.

• The adverse drug reactions are very rare.
THANK YOU FOR YOUR ATTENTION