

XXII World Allergy Congress  
Drug Allergy: Management of Drug Hypersensitivity

## Intra-Operative Reactions

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## INTRAOPERATIVE HYPERSENSITIVITIES

### EPIDEMIOLOGY

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### Incidence of anaphylaxis during GA

**1- In France:**

- ✓ 8 millions GA per year, 2.5 millions with NMBAs
- ✓ 1/10,000-20,000 GA
- ✓ 72.2% IgE-dependent (NMBAs used in 50%)
- ✓ 5-10 per anæsthetist for his/her all life

**2- Same in UK, New Zealand, Australia, Norway**

**3- With major differences in the causes** (no latex in UK and Norway, less NMBAs in Sweden - 8% - 1/60,000)

**4- Mortality: 3.5%** (Australia 1993) - **10%** (UK 2004)

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## Criteria for diagnosing anaphylaxis

- 1 - Typical clinical symptoms (classified according to Ring & Messmer)
- 2 - Other explanations unlikely
- 3 - Positive skin tests
- 4 - Laboratory confirmation criteria :
  - High serum level of tryptase or histamine
  - Positive specific IgE to NMBA's or latex

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## Estimated annual incidence of IgE-mediated allergic reactions during anaesthesia

Causal agents	Estimated annual number of case	Estimated annual incidence in France (/million median [5th-95th perc])		
		Male	Overall	Female
<b>Overall</b>	780 [555-1005]	55.4 [42.0-69.0]	<b>100.6 [76.2-125.3]</b>	154.9 [117.2-193.1]
<b>NMBA's</b>	458 [326-590]	105.5 [79.7-132.0]	<b>184.0 [139.3-229.7]</b>	<b>250.9 [189.8-312.9]</b>
<b>Latex</b>	155 [110-200]	32.6 [24.7-40.5]	<b>59.1 [44.8-73.6]</b>	91.0 [68.9-113.4]
<b>Antibiotics</b>	101 [72-131]	-	-	-
<b>Others agents</b>	80 [57-103]	-	-	-

Mertes JACI, 2011  
1997-2004 GERAP data, France

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## Agents involved in IgE-mediated hypersensitivity reactions during anaesthesia (1837 substances, 1816 patients)

Causal agents		%	Number of patients
<b>Neuromuscular blocking agents</b> (n = 1067, 58.08%)	Succinylcholine	33.40	356
	Rocuronium	29.30	313
	Atracurium	19.30	206
	Vecuronium	10.20	109
	Pancuronium	3.60	38
	Mivacurium	2.50	27
	Cisatracurium	1.70	18
<b>Latex</b> (n = 361, 19.65%)			361
<b>Antibiotics</b> (n = 236, 12.85%)	Penicillin		115
	Cephalosporin		88
	Others		33
<b>Hypnotics</b> (n = 43, 2.3 %)	Propofol	55.80	24
	Midazolam	32.60	14
	Pentothal	9.30	4
	Ketamine	2.30	1
<b>Opioids</b> (n = 31, 1.69%)	Morphine	35.5	11
	Fentanyl	22.6	7
	Sufentanil	22.6	7
	Nalbuphine	12.9	4
	Remifentanyl	6.5	2

Mertes JACI, 2011  
1997-2004 GERAP data, France

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**Agents involved in IgE-mediated hypersensitivity reactions during anaesthesia (1837 substances, 1816 patients)**

Causal agents		%	Number of patients
<b>Colloids</b> (n = 63, 3.43%)	Gelatine	88.9	56
	Hetastarch	9.5	6
	Albumin	1.6	1
<b>Local anaesthetics</b> (n = 6, 0.33%)	Bupivacaine	50.0	3
	Lidocaine	33.3	2
	Mepivacaine	16.7	1
<b>Other agents</b> (n = 44, 2.40%)	Patent blue	25.0	11
	Methylene blue	2.3	1
	Propacetamol	20.5	9
	Aprotinin	11.4	5
	Protamin	9.1	4
	NSAIDs	6.8	3
	Papain	6.8	3
	Nefopam	4.5	2
	Ethylene oxide	2.3	1
	Steroids	2.3	1
	Hyaluronidase	2.3	1
	Metabisulfate	2.3	1
	Povidone	2.3	1
Radio contrast media	2.3	1	

Merfès JACI, 2011  
1997-2004 GERAP  
data, France

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**INTRAOPERATIVE HYPERSENSITIVITIES**

**DIAGNOSIS**

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**Clinical tools for drug anaphylaxis**

✓ **Clinical history:** Demoly et al. for EAACI-ENDA. Allergy 2001

- mandatory
- all drugs and materials used

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## The context of general anaesthesia

### • Difficult context:

- Skin often not visible (operative fields)
  - Urticaria rare in the beginning
  - Patient unconscious
  - Bronchospasm = increase airway resistance
  - Negative inotropic drugs
  - Weak training regarding anaphylaxis
- ➔ **Often not identified  
Few surveys**



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## Anaphylaxis is not easy to recognize

### Should first be eliminated:

- ▶ too light GA
- ▶ bronchial hyperreactivity
- ▶ toxicity of the drugs (LA)
- ▶ other complications...



rapidly think about anaphylaxis, stop the suspected culprit agent, inject adrenaline, measure serum histamine and tryptase, stop surgery if too severe, demonstrate mechanism and cause later on...

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## Allergy consultation

### • If possible in a specialized center:

- Get the operating charts (copies of the originals and not reports)
- Get results from serum analyses (and their timing)
- Describe symptomatology, chronology, severity
- Describe context, background

### • Organize testing:

- Skin tests (with all utilized products) following ENDA-SFAR guidelines
- Measure tryptasemia (if measured at the acute phase and not later on), specific IgE (NMBAs, latex, chlorhexidine...)
- Propose provocation test (AB...) if needed

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## Clinical tools for drug anaphylaxis

✓ **Clinical history:** Demoly et al. for EAACI-ENDA. Allergy 2001

- mandatory
- all drugs and materials used

✓ **Skin tests:**

- **standardized:** Brockow et al. for EAACI-ENDA. Allergy 2002
- **best for general anaesthetics and  $\beta$ -lactams:** Blanca et al. Allergy 2009 and Mertes et al. JIACI 2005 for EAACI-ENDA

✓ **Provocation tests:**

- **standardized:** Aberer et al. for EAACI-ENDA. Allergy 2003
- **rarely needed here:** Torres et al. Allergy 2001; Messaad et al. Ann Intern Med 2004...

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## Skin tests are helpful

✓ **Variable according to the drug involved**

✓ **Best for NMBA, latex and  $\beta$ -lactams:**

- **standardized:** Torres et al. for EAACI-ENDA. Allergy 2003 (indications, precautions, technique, interpretation of the results)
- **immediate reactions:**
  - **NMBAs:** 93% sensitivity and 97% specificity for prick and ID tests with the 7 NMBAs: Mertes Anesthesiology 2003
  - **Penicillins:** 70% sensitivity and 97% specificity for prick and/or ID tests with 4 determinants: Torres et al. Allergy 2001
  - **Cefalosporins:** 86% sensitivity for prick and/or ID tests with the culprit cefalosporin (alone for 2/3): Antunez JACI 2006

✓ **Small case series and many case reports with other drugs, including dyes, RCM**



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INTRAOPERATIVE HYPERSENSITIVITIES

PREVENTION

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## Practical aspects: prevention measures

- **Always get the medical history:** whenever possible, ask specific questions regarding previous allergies (*30% of latex anaphylaxis are avoidable, previous reaction during an anaesthesia, antibiotic allergy...*)
- **Test properly if time, avoid major allergens if no time, also consider regional anaesthesia**

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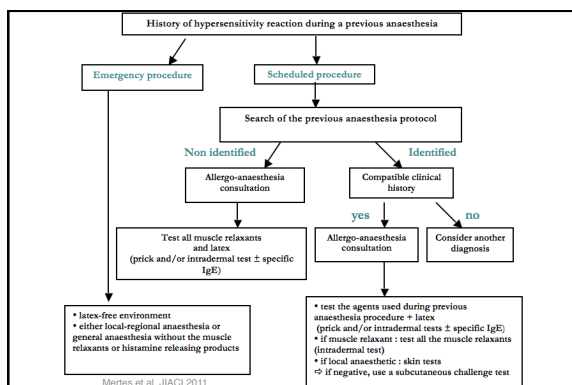
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## Practical aspects: prevention measures

- **Always get the medical history:** whenever possible, ask specific questions regarding previous allergies (*30% of latex anaphylaxis are avoidable, previous reaction during an anaesthesia, antibiotic allergy...*)
- **Test properly if time, avoid major allergens if no time, also consider regional anaesthesia**
- **At the population level:** forbid PHO in OTCs, promote latex-free environments, train anesthetists, promote anaphylaxis network and research

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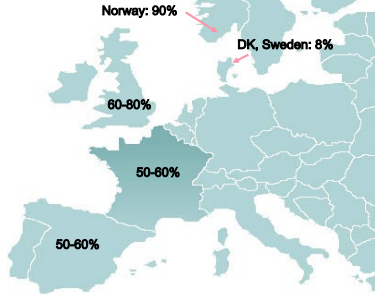
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### NMBA anaphylaxis (relative frequencies)




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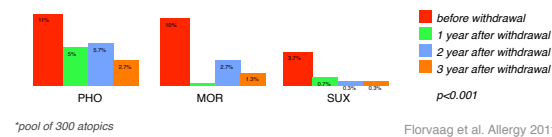
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### Norway: effect of Tuxi<sup>®</sup> withdrawal and IgE sensitization

- Number of NMBA anaphylaxis (*Tuxi<sup>®</sup> withdrawn in March 2007*):

	2005	2006	2007	2008	2009	2010 first 6 month	Trend	P-value	P-value Linear by trend
Total	94	89	81	88	53	25	-0.116	<0.001	<0.001
NMBA	57	62	56	66	34	18	-0.089	0.020	0.018
≠ SUX	11	18	12	15	3	2	-0.196	0.021	0.017*

- Specific IgE\* before - after withdrawal:



\*pool of 300 atopics

Florvaag et al. Allergy 2011

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### Conclusions

- ✓ **Drug anaphylaxis during GA is a rare event** (anesthetists must be prepared)
- ✓ **Drug allergy work up help to find the culprit agent since several causes are possible and to guide the choice of future therapies** (cross-reactivities)
- ✓ **Thorough and standardized procedures generate new scientific knowledge** (database, etiologies, risk factors and prevention measures)

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