진료현장에서 알아야 할 약물부작용과 대처

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주요가이드라인 Drug-Drug Interactions

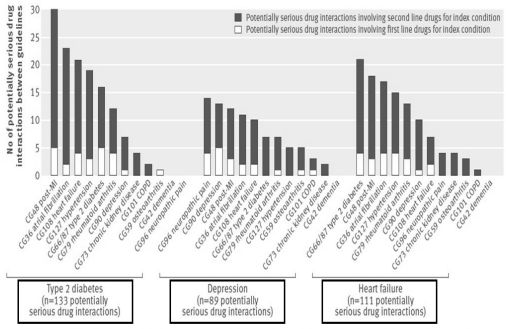


Fig 2 | Potentially serious drug-drug interactions between drugs recommended by clinical guidelines for three index conditions and drugs recommended by each of other 11 other guidelines

Dumbreck S, et al. BMJ 2015

주요가이드라인 Drug-Drug Interactions

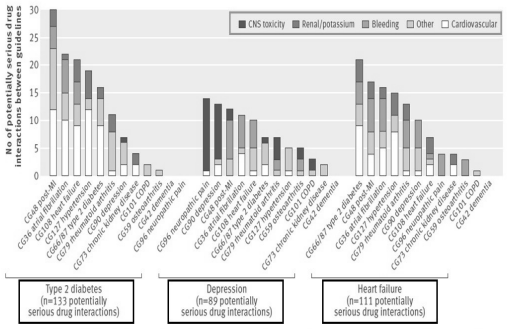
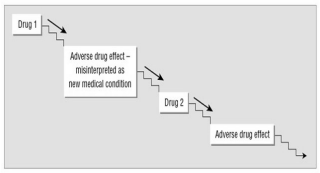


Fig 3 | Types of potentially serious harm from drug-drug interactions between drugs recommended by clinical guidelines for three index conditions and drugs recommended by each of other 11 other guidelines

Dumbreck S, et al. BMJ 2015

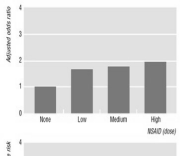
Prescribing cascades

- The **"prescribing cascade"** begins when **an adverse drug reaction is misinterpreted as a new medical condition.**
- Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment.



Rochon RA, et al. BMJ 1997

Prescribing cascades



Examples of prescribing cascade

Initial treatment | Adverse effect | Subsequent treatment

약물유해반응의 분류

Type A (예측가능)	Type B (예측 불가능)
• 70~80% • 고유약리작용과 관련 • 용량에 비례 • 모든 사람에서 가능	• 20~30% • 고유약리작용과 무관 • 용량에 비례하지 않음 • 일부 취약인에서 발생
• Overdose: toxicity • Side effects • Secondary or indirect effects • Drug-drug interaction	• Intolerance • Idiosyncratic reactions • Pseudoallergic reactions • Allergic (hypersensitivity) reactions

약물유해반응의 인과관계 평가

1. **Timing** of the event, relative to the drug exposure
2. Presence or absence of **other factors** which might also cause the event
3. Result of **withdrawing** the drug (de-challenge)
4. Result of **reintroduction** the drug (re-challenge)
5. **Other data** supporting an association, e.g. previous cases.

Nelson Irey (1976), Karch and Lasagna (1977)

UMC causality categories

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically • Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

강의 내용

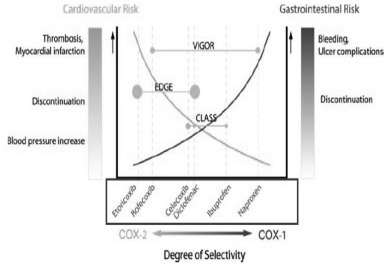
- 약물 동태와 유해반응
- 약물 유해반응의 기전과 분류
- **흔한 약물부작용과 대처**
  - NSAID, 항생제
  - 고혈압, 당뇨, 고지혈증 약제
  - 기타

1) NSAIDs 라벨의 경고 문구 강화 내용

- The risk of heart attack or stroke can occur **as early as the first weeks**
- The risk appears **greater at higher doses**
- Information is not sufficient to determine that the risk of **any particular NSAID** is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients **with or without heart disease or risk factors** for heart disease.
- In general, **patients with heart disease or risk factors** for it have a greater likelihood of heart attack or stroke following NSAID use.
- Patients **treated with NSAIDs following a first heart attack** were more likely to die after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased **risk of heart failure** with NSAID use

2015 FDA Safety Announcement

Selectivity에 따른 심혈관계/위장관계 부작용



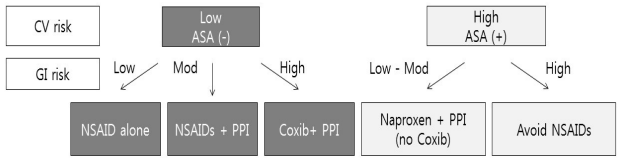
- Selectivity for COX-2 : 심혈관계 위험 증가
- Selectivity for COX-1 : 위장관계 위험 증가

2007 AHA Scientific Statement

Table 2. **Summary of recommendations for prevention of NSAID-related ulcer complications**

	Gastrointestinal risk[a]		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk[b] (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

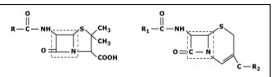
[a]Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). [b]High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori* and if the infection is present, eradication therapy should be given.



NSAIDs 부작용 – 기타

- Hepatotoxicity
- Anaphylaxis
- Pulmonary – AERD, Bronchospasm
- Hematologic – anemia, neutropenia
- CNS – psychosis, aseptic meningitis, tinitus
- Skin reaction – **TEN, SJS**
- Non union – bone, tendon

2) β-lactam Allergy



5) Clinically Significant Drug Interactions

Warfarin + Antibiotics

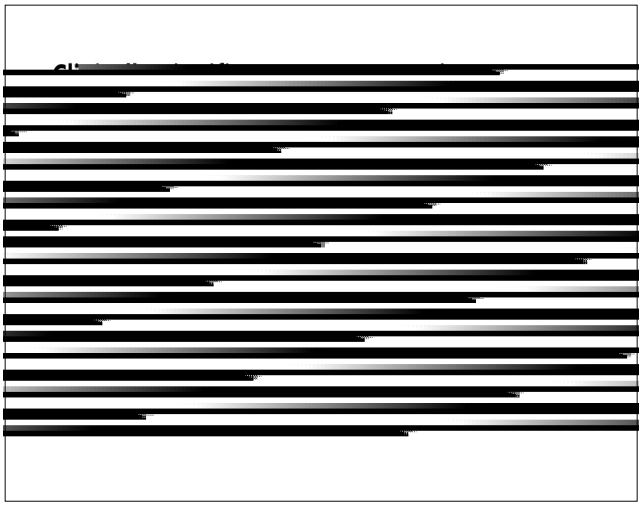
Inhibition of the hepatic metabolism of warfarin

Drugs that inhibit warfarin's metabolism include **ciprofloxacin, clarithromycin, erythromycin, metronidazole and trimethoprim-sulfamethoxazole.**

Unless the prothrombin INR can be monitored every other day, **ciprofloxacin, macrolide antibiotics, metronidazole and trimethoprim-sulfamethoxazole** generally should not be prescribed to patients who are taking warfarin.

Alternative antimicrobial therapy is recommended for these patients.

Ament PW, et al. Am Fam Physician 2000



6) T cell 매개 피부 증상 (Drug eruption)

발진, 發疹 (Exanthem)

- 가장 흔함 ~80%
- 대개 약물 투여 **1주일** 이내
- measles-like (morbilliform) or erythematous maculopapules
- 체간이나 압력, 손상 받은 부위에서 시작하여 전신에 발생
- 대칭적, 여러 개가 합쳐질 수 있다.
- 가렵다.
- 대부분 기전을 모름
- Mononucleosis, **allopurinol** 복용 중인 사람에서 **ampicillin** 투여시 50-80%, HIV 감염에서 bactrim 사용시

7) 요오드화 조영제에 의한 즉시형 과민반응

- 비반세포에서 염증물질 유리
- 임상양상
  - 경증 피부반응 ~ 아나필락시스
  - 투여 후 5-15분 경에 발생하여, 30-60분 경 소실
  - 비 IgE 매개반응: 첫번째 노출에도 발생
  - IgE 매개반응: 조영제 간 교차반응 낮음 (조영제 선택이 중요)
- 빈도

	가려움증, 두드러기	아나필락시스
이온성	6%	0.071%
비이온성	**0.9%**	**0.035%**

- 위험인자
  - 조영제 과민 병력, 천식, 아토피 소인
  - β-차단제나 ACE 억제제 사용, 심혈관계 질환

8) Potentially Inappropriate Medication Use in Older Adults

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

약물 상호반응 및 부작용 검색

- **심사평가원 DUR**
  - https://www.hira.or.kr/rg/dur/form.do?pgmid=HIRAA030033000000
- **약품정보검색**
  - Kims online
  - Drug Info
- FDA
- Pubmed
- **Medscape**
  - Drug interaction checker