Pharmacist's intervention in anticoagulation therapy in hospitals experience and outcomes

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Implementation of the First Pharmacist-Managed Ambulatory Care Anticoagulation Service in Korea

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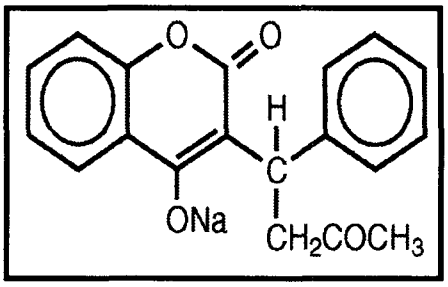
PART I

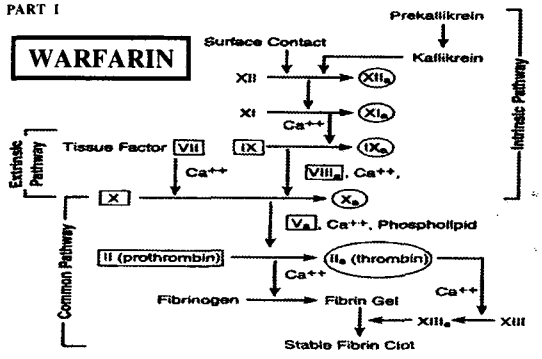
WARFARIN



3-(α-acetonylbenzyl)-4-hydroxycoumarin

PART I

WARFARIN



Simplified clotting cascade. Components in ovals are influenced by heparin; components in boxes are influenced by warfarin.

PART I

WARFARIN

- **Dosing**

  Usual oral maintenance range is 2 to 10 mg/day, titrated to a dose that maintains prothrombin time at a value 1.2 to 2 times control or an international normalized ratio of 1.5 to 3.5 (2.0 to 3.0 INR for most indications)

PART I

WARFARIN

- **Pharmacokinetics**

  A : oral absorption - rapid , BA - excellent, onset - within 36 to 72 h

  D : protein binding - 97 to 99%
  Vd - 0.11 to 0.2 L/kg , $T_{1/2}$ - 20 to 60 h

  M: liver (CYP2C9)

  E : bile, urine

PART I

WARFARIN

- **PT (Prothrombin time) Test**

$$\text{INR} = \frac{\text{Patient PT}^{\text{ISI}}}{\text{Mean normal PT}}$$

INR = International Normalized Ratio
ISI = International Sensitivity Index

PART I

WARFARIN

- Drug-Drug Interactions

DRUG	that Increase PT
O Increased metabolism of vitamin K-dependent clotting factors	Androgens, Thyroid hormones
O Inhibition of warfarin metabolism	Allopurinol, Alcohol (acute), Erythromycin, Amiodarone, Cimetidine, Fluconazole, Metronidazole

PART I

WARFARIN

- Drug-Drug Interactions

DRUG	that Increase PT
O Additive anticoagulant effect	Cephalosporins, Heparin

PART I

WARFARIN

- Drug-Drug Interactions

DRUG	that Decrease PT
O Increased synthesis of vitamin K-dependent clotting factors	Estrogens, Propylthiouracil, Vitamin K
O Induction of warfarin metabolism	Barbiturates, Carbamazepine, Alcohol (chronic), Carbamazepine, Rifampin, Rifampin

PART I

WARFARIN

- Drug-Drug Interactions

DRUG	that Decrease PT
O Decreased absorption of warfarin	Cholestyramine

DRUG	Increased Risk of Bleeding
O Aspirin, NSAIDs, Ticlopidine, Clopidogrel	

PART I

WARFARIN

- Drug-Disease Interactions
  - ✓ Peptic ulcer disease
  - ✓ CHF
  - ✓ Liver disease

PART I

WARFARIN

- Drug-Food Interactions
  - ✓ Foods with substantial vitamin K content
    - green vegetables
    - soybean-based food
    - liver
  - ✓ Nutritional supplements with Vitamin K

PART I

WARFARIN

- **Adverse Drug Reactions**
  - ✓ **Hemorrhagic complications (common)**
    - **Epistaxis, bruise, gingival bleeding, conjunctival hemorrhage, hematuria, bloody or tarry stools**
  - ✓ **Necrosis of skin and other tissues (rare)**
  - ✓ **Rash, alopecia (rare)**

PART I

WARFARIN

- **Management of excessive anticoagulation**
  - ✓ **Hold**
  - ✓ **FFP (fresh frozen plasma)**
  - ✓ **Vitamin K (Chest 1998 ; 114 : 458S)**

Management of excessive anticoagulation

Plan

INR above therapeutic range but < 5.0
Hold warfarin

5.0 < INR < 9.0 without bleeding
Hold warfarin and consider K1(1.0-2.5 mg) orally

9.0 < INR < 20 without bleeding
Hold warfarin and give K1(3.0-5.0 mg) orally

INR > 20
Hold warfarin and consider K1(10 mg) IV

PART I

BACKGROUNDS (I)

- In Korea, pharmacists are not integral members of the medical team
- The primary role of pharmacists is to dispense medications : patient counseling is not emphasized
- The physician spends most of the time dealing with the patient's illness and has little time for anticoagulation therapy management or patient education

PART I

BACKGROUNDS (II)

- A typical drug distribution system makes it difficult to adjust warfarin dosages
- Thus, it is necessary to develop and implement Anticoagulation Service (ACS) to provide optimal anticoagulation therapy and continuity of care in the ambulatory setting
- In USA, ACS has been well established and proven to be cost effective since the late 1960's

PART I

ACS OBJECTIVES

- To prevent potential hemorrhagic or thromboembolic events by close patient monitoring
- To develop multidisciplinary team approach to patient care in the ambulatory care setting
- To allow physicians to utilize patient care time more efficiently
- To improve patient compliance through comprehensive **patient education**

PART I

PATIENT EDUCATION

- Indication
- Dosage of warfarin
- Potential adverse reactions
- Potential drug/drug and drug/food interactions
- Importance of anticoagulation therapy, monitoring, and compliance
- PT tests (INR results)

PART I

ACS RESPONSIBILITIES

- Order PT tests
- Provide comprehensive patient education
- Schedule ACS follow-up appointments
- Provide ACS summary sheet to physicians
- Serve as a liaison between health care providers
- Adjust warfarin dose based on clinical indicators

PART I

CLINICAL INDICATORS FOR DOSAGE ADJUSTMENT

- INR results
- Bleeding/Thrombotic events
- Concurrent medications
- Diet changes
- Alcohol intake
- Patient compliance
- Other criteria that may affect anticoagulation therapy

PART I

PATIENT FOLLOW-UP PERIOD

Classifications	Period
Discharged Non steady-state	< 4 Days
Dosage adjustment > 20%	< 7 Days
Dosage adjustment < 20%	10 ~ 14 days
Stabilized	Monthly

PART I

RECOMMENDED THERAPEUTIC RANGE FOR ORAL ANTICOAGULATION THERAPY IN USA

Indication	INR
Venous thrombosis Pulmonary embolism Systemic embolism Tissue heart valves Acute myocardial infarction Valvular heart disease Atrial fibrilation	2.0-3.0
Mechanical heart valves Recurrent systemic embolism	2.5-3.5

PART I

RECOMMENDED THERAPEUTIC-RANGE IN KOREA

- Physicians requested that INRs be maintained between 1.5 and 2.5 when warfarin is used for primary prevention in patients with a high risk of hemorrhage
- For the purpose of the following study, an INR between 1.5 and 3.5 was considered to be therapeutic

IMPLEMENTATION OF ACS AT SMC

PART II

DEVELOPMENT HISTORY

- **1995. 5. 1 – 1995. 7. 31**
  A pilot study in outpatients visiting the cardiology department was carried out
- **1995. 8. 1 – 1996. 4. 30**
  The study was extended using other departments' (thoracic and general surgery, etc.) outpatients
- **1996. 5. 1 –**
  ACS was implemented at SMC

PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

- **All patients were randomly divided into 2 groups; ACS group and Control group**
- **The frequency of INR testing and the percentage of INRs maintained within the therapeutic range were evaluated in the two groups**

PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

- **Number of Patients**

Group	No. of Total Patients	No. of Excluded Patients	No. of Total INR	No. of Excluded INR	No. of Real INR
ACS	62	3	165	68	97
Control	117	0	151	16	135

PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

- **Demographic data**

	ACS	Control
Age	35-75 Y (Mean 59 Y)	21-78 Y (Mean 58 Y)
Sex (Male %)	37 (59%)	67 (57%)
Sex (Female %)	25 (41%)	50 (43%)

PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

- **Indications for oral anticoagulant therapy**

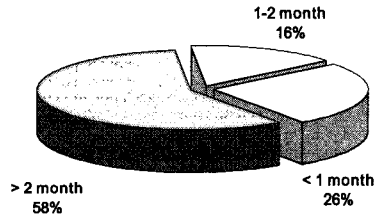
Indications	ACS		Control	
	No.	%	No.	%
Angina pectoris	15	13.5	21	9.7
Myocardial infarct	7	6.3	12	5.5
Atrial fibrillation	23	20.7	82	37.8
Valvular heart disease	16	14.4	48	22.1
Valve replacement	6	6.3	10	4.6
Deep vein thrombosis	3	2.7	4	1.8
Pulmonary embolism	1	1.0	1	0.5
Cerebral infarct	4	3.6	11	5.0
PTCA*	22	19.8	13	6.0
Stent insertion	3	2.7	7	3.2
Miscellaneous	8	9	8	3.8

*PTCA : Percutaneous Transluminal Coronary Angioplasty

PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

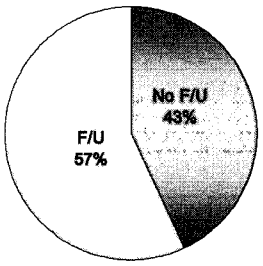
Duration of PT F/U (Control)



PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

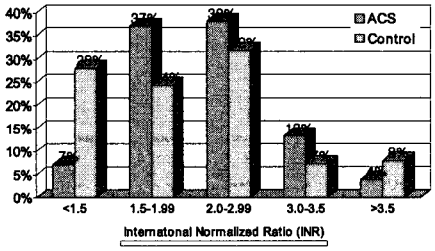
PT F/U per Rx Refill (Control)



PART II

PILOT STUDY (1995. 5. 1 – 7. 31)

Comparison of INR between ACS and Control Group



PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

- **Number of Patients**

ACS	Control
230	450

Outpatient : 56.3%

Inpatient : 43.7%

PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

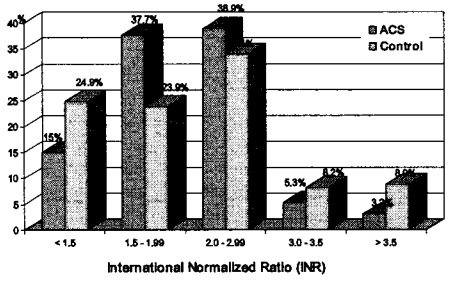
- **Indications for oral anticoagulant therapy**

Indications	No.	%	Indications	No.	%
Myocardial infarct	92	23.4	CHF	25	6.4
Atrial fibrillation	70	17.8	DVT	18	4.6
Valvular dysfunction	54	13.7	Stroke	13	3.3
PTCA	53	13.5	LA, LV thrombi	7	1.8
Valve replacement	28	7.1	PE	3	0.8
Stent	27	6.9	Miscellaneous	3	0.8

PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

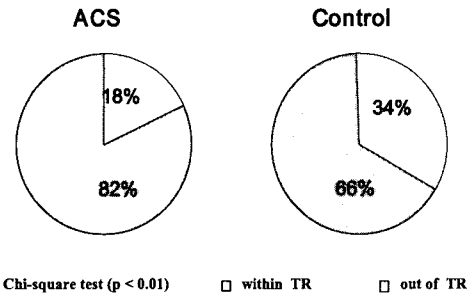
Comparison of INR between ACS and Control Group (I)



PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

Comparison of INR between ACS and Control Group (II)



PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

- **Adverse effects -total 54 cases in 49 patients**

Bruise : 16 cases (29.6%)
Nose bleed : 13 cases (24.1%)
Occular hemorrhage : 8 cases (14.8%)
Increased mens amount : 7 cases (13.0%)
Gingival bleeding : 3 cases (5.6%)
Blood sputum : 1 case — Urinary bleeding : 1 case
Blood stool : 1 case — Hematoma : 1 case
PE : 1 case — LA thrombi : 1 case
Intracranial hemorrhage : 1 case

PART II

EXTENDED STUDY (1995. 5. 1 – 1996. 4. 30)

- **Drug Interactions**

Drug	INR	case
Antibiotics (cold meds)	↑	5
Herb medication	↓	3
Cimetidine	↑	2
Lovastatin D/C	↓	2
Doxycycline	↑	1
Miscellaneous	↑	3
Total		16

CONCLUSIONS

- The 3-month pilot study demonstrated that the first pharmacist-managed anticoagulation service improved therapeutic outcomes in patients taking warfarin
- The percentage of INRs maintained within the therapeutic range in the ACS group was 82%, versus 66% in the Control group
- The anticoagulation service managed by pharmacists was successfully implemented at SMC
- As of today, over 1,800 patients from 10 departments have been enrolled and actively cared by the clinical pharmacists

ACS-Operating Hospitals in Korea (1)

2004. 5 기준

Initiation Date	Hospital	Counseling	Dosage Adjustment
1995. 5	SMC	O	O
1996.12	Kangdong SungShim	O	O
1997. 3	SNUH	O	O
1998. 7	Kangbok samsung*	O	O
1999. 3	Severance (YD)	O	X
1999. 4	Korea University (Guro)	O	O
1999. 5	Paik (Pusan)	O	O
1999	CMC	O	X
1999	Severance (SC)	O	X

* Discontinuated 2000.7

ACS-Operating Hospitals in Korea (2)

Initiation Date	Hospital	Counseling	Dosage Adjustment
2000. 4	CMC (Yeouido)	O	X
2000. 6	Kyungpook University*	O	O
2000	Inha University	O	X
2001	Buchon Sejong	O	O
2001. 7	Taegu Fatima	O	O
2002. 1	Pusan University	O	O
2002. 1	Korea University(AA)	O	O
2002(Mid)	Chungnam University	O	X
2003. 2	CMC(Chung ju)	O	X
2003. 4	Kangnamg SungShim	O	X
2003. 4	AMC	O	O

* Discontinuated 2000.7


Thank You