

USE OF UNFRACTIONATED HEPARIN TO REDUCE VENOUS THROMBOEMBOLISM IN PATIENTS
WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE: RESULTS FROM A SINGLE-CENTER
RETROSPECTIVE COHORT STUDY

BY

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ABHIJIT VIJAY LELE

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and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the
degree of Master of Science.

Chairperson, Theresa I Shireman, Ph.D., RPh

Milind A Phadnis, Ph.D.

Paul J Camarata, M.D

Date Defended: January 5, 2015

The Thesis Committee for ABHIJIT VIJAY LELE certifies that this is the approved version of the
following thesis:

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A handwritten signature in cursive script, reading "Theresa I Shireman", is written above a horizontal line.

Chairperson, Theresa I Shireman, Ph.D., RPh

Date approved: January 8, 2015

Abstract

Introduction

Patients with aneurysmal subarachnoid hemorrhage (a-SAH) are at high risk for venous thromboembolism (VTE). While risk factors for VTE in this patient population are well known, there is currently paucity of data regarding optimal chemical prophylaxis practices, and it is left to individual provider to decide on drug, dose and timing of initiation of chemical prophylaxis.

Purpose of the study

The University of Kansas Medical Center's dedicated neurocritical care unit implemented a VTE prophylaxis protocol in 2011. This study was undertaken to gain insight into unfractionated heparin utilization practices following the adoption of this protocol and its effect on incidence of VTE events over 5 years as a quality improvement initiative.

Materials and methods

A retrospective cohort study was conducted on patients with confirmed SAH after cerebral aneurysm rupture admitted between July 1, 2008 and December 31, 2013. Exposure of interest was unfractionated heparin, and the outcome measures were venous thromboembolism events (VTEs), and adverse events due to UFH. Pearson Chi-square test and Student's t-test were used to test differences in utilization, VTE incidence and time to initiation of UFH in time periods before and after implementation of VTE protocol.

Results

There were 124 patients who met inclusion criteria and 94 (75.8%) received chemical prophylaxis. Implementation of VTE prophylaxis protocol led to an increase in UFH utilization from 53.23 % to 98.36% (p-value <0.001). There was concurrent reduction in time to initiation of UFH from 164.9 hours to 92 hours (p-value 0.017). A total of 19 VTE events (15.32 % incidence) were identified in our study cohort, with a decreasing trend in VTE incidence from 17.74% to 13.11 % (p-value 0.48). Adverse events (7.4%) noted with use of UFH included;

retroperitoneal hematoma (2 events), heparin induced thrombocytopenia (3 events), worsening of pre-existing hemorrhage (1 event), and hemorrhage along external ventricular track (1 event). None of the adverse events related to UFH were fatal.

Conclusions

Implementation of VTE prevention protocol resulted in increased use of unfractionated heparin, which coupled with reduction in time to initiation of unfractionated heparin led to a reduction of venous thromboembolism, with lower incidence of adverse events.

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Introduction

Aneurysmal subarachnoid hemorrhage (a-SAH) affects approximately 30,000 Americans each year. It is a disease with high mortality and morbidity. For those who survive the initial insult, however, there is subsequent risk for additional morbidity and mortality from venous thromboembolism events (VTEs), which occur in 3.8-18% of patients¹⁻⁴. The challenge for the clinician is balancing the need to control and repair the initial hemorrhage with adequate prevention of these significant thrombotic events.

VTEs occur due to hypercoagulability, hemodynamic changes (stasis, turbulence) and endothelial injury/dysfunction, the three cardinal factors that define Virchow's triad⁵. It is postulated that central sympathetic activity and clinical manifestations of non-adrenergic activity also contribute to increased incidence of VTE⁶. In general, patients with subarachnoid hemorrhage are at high risk of VTE due to decreased level of consciousness, need for mechanical ventilation, and limb weakness, making them ineligible for ambulation.

Guidelines for management of aneurysmal subarachnoid hemorrhage^{7,8} acknowledge the frequency of VTEs and discuss the lack of evidence for screening parameters. There are no explicit guidelines for selecting an appropriate VTE preventive measure, leaving individual physicians to decide between surgical compression devices and appropriate anticoagulation.

Sequential compression devices (SCDs) or antiembolic stockings (AES) are applied to the calves of patients with a-SAH immediately upon admission and are considered standard of care though they fail to prevent all VTEs. When faced with a patient who may be at high risk of re-bleeding into the brain, it is not practical to start chemical prophylaxis (unfractionated heparin or low molecular weight heparin) until the bleed is stable. In fact, early hours after subarachnoid hemorrhage are focused on reversing coagulopathy, diagnosing and treating ruptured cerebral aneurysm, and performance of invasive procedures such as craniotomy and placement of intracranial pressure monitoring devices, and cerebrospinal fluid drains. It is only after bleeding is stable, and a period of

observed “stability” passes that a physician is truly comfortable with initiation of chemical prophylaxis.

While the risk factors and incidence of VTE in patients with a-SAH are well known, safety and efficacy of unfractionated heparin (UFH) in reduction of VTE is unknown. A hospital-wide VTE task force established at our institution identified VTEs in patients with a-SAH as a key quality improvement measure. We subsequently instituted a VTE prevention protocol in year 2011 in our neurocritical care unit where daily assessments would be performed by neurointensivists and neurosurgeons. SCDs would be used in all patients? The decision to anticoagulate with UFH took into consideration the risks and benefits of chemical prophylaxis for specific patients.

Unfractionated heparin with its shorter duration of action and ease of reversibility makes it an attractive option for chemical prophylaxis in situations where urgent reversal of its effects needs to be performed to prevent catastrophic hemorrhagic complications. This study was performed to evaluate the adoption of this internal guideline and examine the rate of VTE development over a five-year period.

We hypothesized that unfractionated heparin (5000 units administered subcutaneously every 8 hours) in addition to SCDs would further reduce the risk of VTE. Results from our study may provide valuable information about beneficial effects of chemical prophylaxis in the reduction of VTE as well as highlight commonly seen adverse effects, and also help us gain insight into practices about timing of initiation of chemical prophylaxis in patients with a-SAH.

Methods

We performed a retrospective cohort analysis of patients with aneurysmal subarachnoid hemorrhage, identified from a subset of patients admitted with diagnosis of subarachnoid hemorrhage (ICD9 430) between July 1, 2008 and December 31, 2013. We assessed the adoption of UFH and time to its initiation and the occurrence of venous thromboembolism events (VTEs) and reports of adverse effects related to unfractionated heparin.

Cohort creation

After review of electronic medical records, we created a cohort consisting of patients above the age of 18 years, with a proven subarachnoid hemorrhage caused by a ruptured cerebral aneurysm, without persistent coagulopathy which was defined as INR > 1.5 or platelet count below 100,000, and excluded those who died within 24 hours of admission and those whose hospital course was of a palliative nature with no expectations of aggressive medical or surgical intervention as established in goals of care. Patients who had documented allergies to UFH were also excluded from this study, as were patients with pre-existing deep venous thrombosis prior to admission.

Covariates and descriptive variables

Demographics and clinical variables, collected from patients' medical records included age, sex, race by ethnicity, smoking, body mass index (BMI), comorbidities, and severity of subarachnoid hemorrhage. Race was categorized into White and Non-White. Body mass index (BMI) was classified into BMI < 30 kg/m², and > 30 kg/m². Well-defined and previously used grading scales such as Hunt and Hess ⁹ and Modified Fisher score ¹⁰ quantified severity of subarachnoid hemorrhage. Patients were classified as good grade subarachnoid hemorrhage for Hunt Hess I, II & III, and Modified Fisher I & II as previously described. Comorbidities consisted of hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, chronic atrial fibrillation, and renal insufficiency.

Medication exposure

Patient charts and hospital electronic records were reviewed to obtain patient information with respect to the use of 5000 units of UFH administered subcutaneously every 8 hours. Proportion of patients receiving UFH was measured and expressed for every year of study participation. Actual time of administration of UFH captured enabled us to calculate time to initiation of UFH, which was recorded in hours. Patients were grouped depending on their exposure to UFH at any given point during their hospital stay into UFH and non-UFH groups to report descriptive statistics.

Outcomes

Primary outcome included VTE occurrence. VTE was defined as the demonstration of occlusion of deep veins of upper or lower extremities on Doppler venous sonography, or demonstration of pulmonary embolism on computed tomographic angiogram of the lungs. Superficial vein thrombosis and chronic scarring of veins were excluded. Actual time of performance of Doppler examination or CT scan enabled us to calculate time to VTE event, which was recorded in hours.

Incidence of VTE was calculated based on number of new VTE events diagnosed per year per patients admitted and was recorded for every year of study participation.

Secondary outcome included adverse events associated with the use of unfractionated heparin. Intracranial adverse events were defined as new hemorrhage or worsening of pre-existing hemorrhage as reported on CT scans of the brain performed after initiation of chemical prophylaxis. Extracranial adverse events studied included development of heparin-induced thrombocytopenia (HIT), or anemia defined as hemoglobin under 10 gm/dl following initiation of chemical prophylaxis, formation of inguinal hematoma, muscle hematomas or retroperitoneal hematomas developing after initiation of UFH.

Statistical analysis

Continuous variables such as age, time to initiation of heparin (hours), and time to diagnosis of VTE event (hours) were expressed in mean and standard deviation. Categorical variables were expressed in terms of their frequency and counts. For categorical variables Chi-Square test was performed, while for continuous variables Student's t-test was performed. As we had a small sample size and few VTE events, analyses were limited to descriptive associations.

Statistical significance was inferred when $p < 0.05$. Data was analyzed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

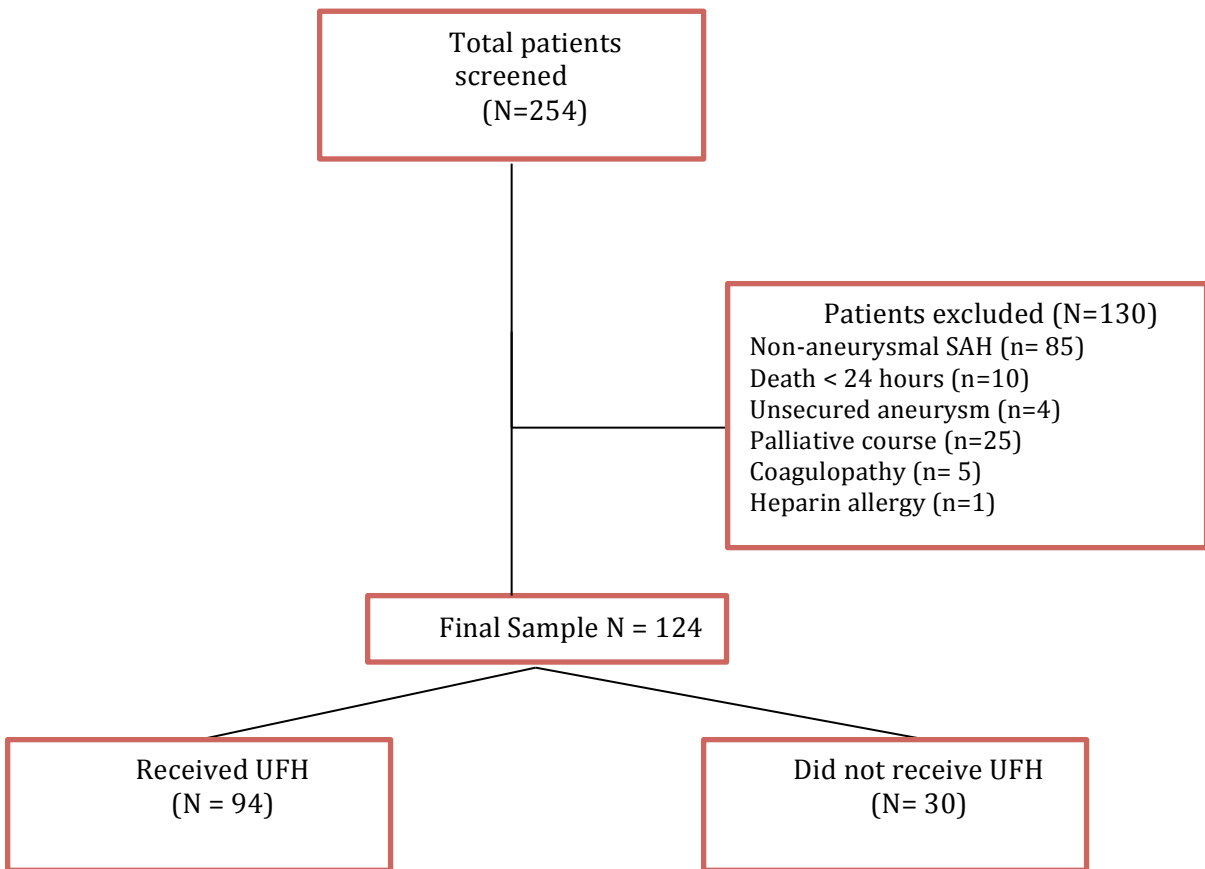
Compliance and Research Participation Protection

This project was approved as an expedited review by the institutional review board at the University of Kansas Medical Center (KUMC).

Results

Of the initial 254 patients with subarachnoid hemorrhage screened for eligibility, 124 patients were included for final analysis. More than three-fourths (75.8 %, or 94) received UFH during the window of observation. There were 30 patients who had no exposure to UFH (Figure 1).

Figure 1. Flowchart demonstrating creation of the study cohorts for patients with aneurysmal subarachnoid hemorrhage



The baseline characteristics of the two cohorts exposed and not exposed to UFH are shown in Table 1. In both analytic cohorts, patients were predominantly female, less likely to be Non-White, had BMI <30, were chronically hypertensive, active smokers, and more likely to be admitted in good clinical and poor radiographic grade subarachnoid hemorrhage. Hypertension and active smoking was more prevalent in those who received UFH.

Table 1: Descriptive characteristics of patients with and without exposure to UFH among patients with aneurysmal subarachnoid hemorrhage

	UFH	Non UFH
	N=94	N=30
Age (years)(SD)	53.9(13.8)	54.8(14.8)
Sex		
Male	29(30.8%)	8(26.7%)
Female	65(69.2%)	22(73.3%)
Race (White)		
White	62(66%)	22(73.3%)
Non-White	32(34%)	8(26.7%)
Body mass index		
BMI < 30	69(73.4%)	23(76.7%)
BMI > / = 30	25(26.6%)	7(23.3%)
Co-morbidities		
Chronic hypertension *	52(55%)	9(30%)
Diabetes Mellitus	12(12.8%)	3(10%)
Hyperlipidemia	18(19.1%)	5(16.7%)

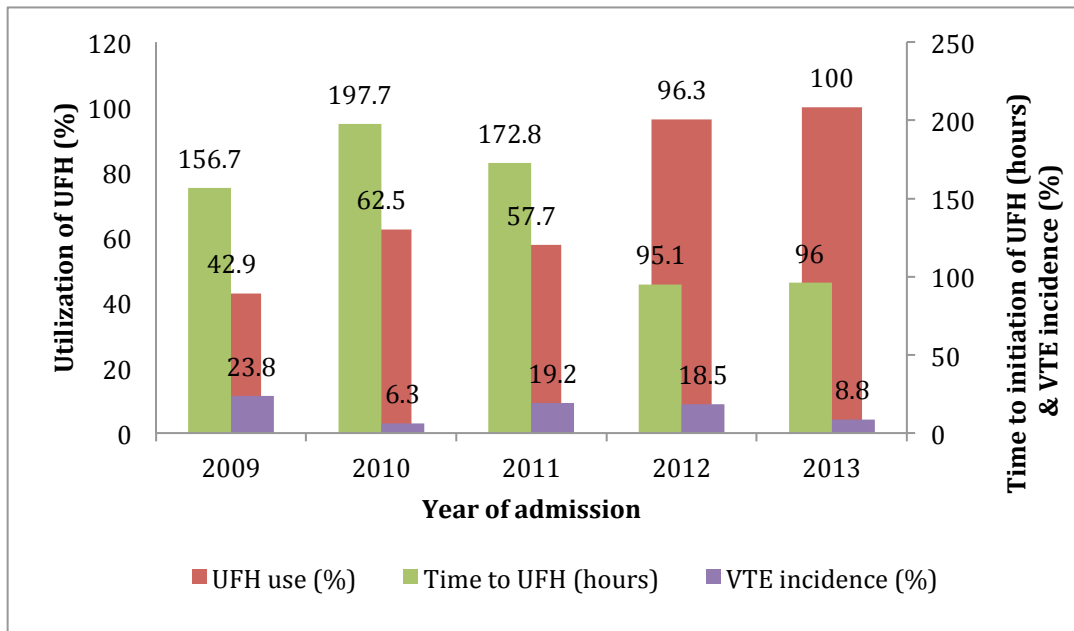
Coronary artery disease	1(1%)	2(6.7%)
Chronic Atrial fibrillation	2(2.1%)	0
Active smoker	24(25.3%)	8(26.7%)
Former smoker	7(7.4%)	1(3.3%)
Renal insufficiency	5(5.3%)	0
Pre-admission medications		
Anti-coagulation / antiplatelet agents	4(4.2%)	1(3.3%)
Clinical severity (Hunt and Hess Grade)		
Good grade (Hunt & Hess I-III)	81(90%)	22(73.3%)
Poor grade (Hunt and Hess IV)	13(10%)	7(26.7%)
Glasgow Coma score (GCS)		
GCS \geq 8	80(85.1%)	23(76.7%)
GCS < 8	14(14.9%)	7(23.3%)
Radiographic severity (Modified Fisher Grade)		
Good grade (Modified Fisher I&II)	32(33.7%)	9(30%)
Poor grade (Modified Fisher III & IV)	63(66.3%)	21(70%)

* p-value < 0.05

We compared use of UFH over five years, and Figure 2 illustrates the increase in proportion of patients receiving UFH, reduction in time to initiation of chemical prophylaxis, and overall reduction in incident VTE events over the study period. In the first year, 42.9% of the SAH cases received UFH, the time until initiation of UFH was 156.7 hours, and 23.8% incurred a VTE. By 2013 we had increased UFH use to cover 100% patients, were able to reduce time to initiation of UFH to 96 hours (p-value 0.1132), and reduced the VTE incidence to 8.8% (p-value 0.3214).

Implementation of VTE protocol resulted in greater utilization of UFH (53.23% to 98.36%, p-value < 0.001), reduction in time to initiation of UFH (162.9 hours to 92 hours, p-value 0.017), and reduction in VTE incidence (17.74 % to 13.11%, p-value 0.48).

Figure 2. Comparative use, time to initiation of UFH, and incidence of VTE events in patients with aneurysmal subarachnoid hemorrhage over time



A total of 19 VTE events were identified during the study period. Of these 19 events (16 as DVT and 3 as PE), 15 were observed in patients who had received UFH at some point during their admission stay. None of the VTE events were fatal.

Of the 19 VTE events, 9 were asymptomatic and were discovered on surveillance Doppler ultrasonography. Fourteen events occurred in patients with high Modified Fisher grade (Grade 4). With respect to method of securement of cerebral aneurysms, 11 out of 19 events occurred in patients who had undergone aneurysm coiling, and the rest of the 8 events, occurred in patients who had undergone aneurysm clipping. The relatively few number of VTE events prevented us from performing multivariate analysis in order to test for effectiveness of UFH in reduction of risk of VTE.

A total of 7 adverse events (7.44%) related to UFH were observed. Retroperitoneal hematoma was seen in 2 patients (2/95, 2.1%), while heparin induced thrombocytopenia was seen in 3 patients (3/95, 3.2%), worsening of pre-existing hemorrhage was seen in 1 patient (1/95, 1.1%), and 1 patient (1/95, 1.1%) experienced new hemorrhage along tract of external ventricular catheter. None of these hemorrhagic complications were fatal.

Discussion

Our research objective was to determine whether implementation of a VTE protocol lead to any reduction in incidence of VTE. We found an overall increase in utilization of UFH, reduction in time to initiation of UFH and a decline in number of VTE events.

We developed a VTE protocol based on existing evidence ¹¹⁻¹⁵. While the protocol was based on evidence not specific for a-SAH patients, it gave us some insight into VTE prevention practices in other disease processes including intracranial hemorrhage. We used the rationale that while sequential compression devices may be used soon upon admission, chemical prophylaxis may be initiated only after ruptured aneurysm is secure, after patient demonstrates stability and the treating primary physician comfortable with use of UFH, with the neurosurgeons having the ultimate authority of withholding chemical prophylaxis. Despite these potential limitations, we were able to achieve a high percentage of UFH use in a-SAH population.

As expected, both study cohorts comprised of females who were hypertensive and active smokers. Whites outnumbered non-Whites across both groups, which is perhaps reflective of our institution's admission demographics.

A high proportion of VTE events were diagnosed on routine surveillance Doppler sonograms of the lower extremities. While the use of surveillance Doppler imaging in patients who are on chemical prophylaxis is debatable, our study results indicate that routine Doppler imaging is still important even in patients receiving chemical prophylaxis, as findings of proximal deep venous thromboses may necessitate placement of vena cava filters in patients not found to be suitable candidates for full anticoagulation, with the goal of prevention of a fatal pulmonary embolism.

While it is interesting to note that majority of VTE events were observed in patients who were exposed to UFH, it is unclear if delayed time to initiation of heparin played any role in development of VTE these patients. This is an area for performance improvement and we intend to look into this in future studies.

As many as 30 patients were never administered UFH during their hospital stay. It may be possible that providers considered continuation of non-pharmacological measures over UFH especially in patients who were ambulatory or closer to discharge. It is possible that these patients may benefit from UFH before discharge. Another area of future performance improvement initiative is to look at 30-day readmission rates for VTE in patients discharged without ever being administered chemical prophylaxis.

It is likely that in our study cohort, careful screening of patients and appropriate time from onset of hemorrhage to chemical prophylaxis resulted in low incidence of adverse events, and it is encouraging that none of the adverse events were fatal. Since majority of the adverse events occurred in patients who had experienced a VTE event, these adverse events pose unique therapeutic challenges, including interruption of UFH for extended period of time, and hesitation on part of physicians to restart any form of anticoagulation, necessitating perhaps placement of inferior vena cava filter.

It is important to consider several limitations of our study. First of all due to small number of VTE events, we were unable to perform multivariate analysis in order to test for true efficacy of UFH in reducing VTE risk. Secondly, in order to test for the efficacy of UFH in patients with a-SAH, it is important to be consistent in time of initiation of UFH. Even when the protocol was implemented, it was still left to the individual practitioners to decide optimal time to initiation of chemical prophylaxis, and we did not control for this variability, which may decrease our ability to generalize findings to the population with a-SAH as a whole. We did not control for factors that may affect patients receiving UFH, e.g., confounding by indication. There may still be some unknown factors, which may affect why certain patients received UFH and the rest did not.

This is a very first study conducted on patients with aneurysmal subarachnoid hemorrhage to understand use of UFH and its effect on reduction of VTE. As neurointensivists and neurosurgeons assess patients daily for initiation of chemical prophylaxis, and meet hospital and

national standards ¹⁶ , it is important to remember that VTE events can occur despite optimal prophylactic measures, and further research may answer the question whether VTE is a never event in patients with a-SAH.

Conclusion

Strict implementation of VTE protocol using unfractionated heparin along with sequential compression devices resulted in greater use and reduction in time to UFH, which in turn may have reduced VTE events with few non-fatal adverse events.

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Appendix

Use of unfractionated heparin to reduce venous thromboembolism in patients with aneurysmal subarachnoid hemorrhage: Results from a single-center retrospective cohort study.

Abhijit V. Lele, M.D., Paul J. Camarata, M.D., Milind A. Phadnis, Ph.D., Theresa I. Shireman, Ph.D., RPh.,

Abhijit V. Lele, M.D., Associate Professor, Departments of Anesthesiology, Neurology & Neurosurgery, The University of Kansas Medical Center, Kansas City, KS.

Paul J. Camarata, M.D., Associate Professor, Department of Neurosurgery, The University of Kansas Medical Center, Kansas City, KS.

Milind A. Phadnis, Ph.D., Research Assistant Professor, Department of Biostatistics, The University of Kansas Medical Center, Kansas City, KS.

Theresa I. Shireman, Ph.D., RPh, Professor, Department of Public Health, The University of Kansas Medical Center, Kansas City, KS.