CARDIOVASCULAR RISKS AMONG TESTOSTERONE DOSAGE FORMS

There are a variety of dosage forms available for testosterone including intramuscular injections, topical gels, transdermal patches, implantable pellets, intranasal sprays, and oral/buccal applications. Each of these dosage forms affects testosterone levels differently. Intramuscular injections create a spike in levels which subsequently decline at a gradual rate. Testosterone gels and transdermal patches result in a slight increase and allow for more consistent levels. However, the gels and patches must be reapplied more frequently than the injection. Testosterone use has increased over the years and is prescribed often without apparent indications. With the increased use, many studies have begun to focus on the safety of testosterone. Recent studies have reported mixed results as to whether testosterone carries a risk for cardiovascular events. Due to the differing effects of dosage forms on testosterone levels, current dosage forms may have a higher risk for cardiovascular events than other forms. This issue of CLIPS briefly summarizes an article that compares the cardiovascular risks among different testosterone dosage forms. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


Methods

- This study was a retrospective cohort study comparing testosterone injection, gel, and patch dosage forms.
- Data was collected from 3 sources:
  - The Truven MarketScan Commercial Claims and Encounters and Medicare Supplementary and Coordination of Benefits to include a commercially insured population of men 18 years and older
  - United States Medicare which used a national random 20% sample of the fee-for-service population consisting of adults 65 years and older
  - The Clinical Practice Research Datalink (CPRD) which contains general practitioner medical records for the United Kingdom including men 18 years and older.
- Men who were starting testosterone therapy after a 180-day testosterone-free washout period were included.
- This study focused on gels, patches, and injections dispensed by a pharmacy along with in-office injections.
- Exclusion criteria: use of implanted pellets, oral/buccal testosterone, or oral methyltestosterone during the washout period and two different testosterone dosage forms recorded on the individual's index day which was defined as the date of the first prescription or in-office injection after the washout period.
- Subjects were monitored for one year to detect any cardiovascular events. These events included myocardial infarction, unstable angina, stroke, composite acute events, all-cause hospitalization, mortality, and venous thromboembolism (VTE). If an outcome occurred during the baseline period, the subject was excluded.
- The MarketScan database was unable to provide mortality data.
- Baseline total serum testosterone tests were conducted and categorized as low, normal, or high. Other covariates evaluated were calendar year, age, comorbidity, cardiovascular risk factors, health care utilization, preventive and screening care, indications for testosterone, and other medication use. Data from the CPRD database also accounted for body mass index and smoking.
- Two separate comparisons were conducted in the study: gels vs. injections and gels vs. patches.
- Due to differences in the databases, analyses were conducted on each database then the adjusted results were meta-analyzed.

Results

- A total of 544,115 new testosterone use patients were included from the 3 databases consisting of 55.8% gel, 37.4% injection, and 6.9% patch users. The majority in the MarketScan population was gel, and injection was most common in the Medicare population. The CPRD database had relatively equal proportions of gel and injection users at 42.4% and 39.6% respectively.

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Results (continued)

- MarketScan had similar results and mean age across the three dosage forms. Majority of the testosterone injections were testosterone cypionate (83.3%).
- Medicare had an older mean age than the other two databases. Patients included from this database experienced an increase in heart failure and psychiatric disorders with the patch compared to the gel and injection patients.
- 1-year incidence of cardiovascular events and mortality were more common in the patients from the Medicare database. The MarketScan and Medicare databases reported more hospitalizations than the CPRD. Results showed low venous thromboembolism (VTE) rates. Lower crude rates were revealed in patients using the gel form compared to patients using the injection or patch.
- In the injection vs. gel comparison, the pooled data showed a statistically significant increase in composite acute events (HR 1.26; 95% CI, 1.18 – 1.35) along with myocardial infarction, unstable angina, stroke, death, and all-cause hospitalization outcomes. VTE outcomes did not have a statistical significance in the pooled data (HR 0.92; 95% CI, 0.76 – 1.11). The adjusted data for MarketScan and Medicare individually reflect this data. However, the only outcome statistically significant from the CPRD in adjusted data was the composite acute events.
- In the patch vs. gel comparison, myocardial infarction and all-cause hospitalization were the only two outcomes with a statistically significant pooled analysis (HR 1.10; 95% CI, 0.94 – 1.29 for cardiovascular events; HR 1.21; 95% CI, 1.01 – 1.43 for myocardial infarction; HR 1.04; 95% CI, 1.00 – 1.08 for hospitalizations). While the MarketScan individual, adjusted data agrees with these results, the Medicare and CPRD data found all outcomes were not statistically significant.
- All sensitivity analysis agreed with the primary analysis. The analysis for mean treatment duration reported durations of 122, 105, and 96 days for the gel, injection, and patch forms respectively.

Discussion

- Injections had a higher risk for cardiovascular events, cerebrovascular events, hospitalizations, and deaths than gels.
- A slight increase in myocardial infarctions was revealed with the use of patches compared to gels.
- No dosage form had a higher risk for VTE over the others based on the data in this study.
- Per 1,000 person years, the Medicare database revealed 23.1 events in gels, 36.6 events in injections, and 34.9 events in patches with the composite acute events outcome.
- A previous CPRD study revealed the possibility of testosterone dosage forms carrying different risk profiles when the injection form had greater hypertension and polycythemia risks than the oral forms.
- Limitations: lack of important patient characteristics, nonrandomized exposure, possible outcome misclassification, smoking and body mass index were not included in the MarketScan and Medicare cohorts, possible differences in behavioral, economic, or social differences, adherence was not analyzed, and people with less disease-management skills may be given injection due in-office administration.
- The CPRD cohort showed that obesity had minimal effect on the outcomes while current smokers did contribute. Nevertheless, the adjusted and crude data for both were similar.
- With a lack of primary indications due to difficulty diagnosing hypogonadism, analysis only included patients where treatment was considered to be required.
- Due to inadequate availability of testosterone levels, impact from certain blood levels could not be determined. Primary analysis was not adjusted for baseline levels.
- The 3 databases provided a diverse patient sample including men of different ages, populations, and practice patterns. With this diverse data, the results were still similar across the 3 databases.

Conclusions

- Short-term risks for a cardiovascular event, stroke, death, and hospitalization appear higher with the use of testosterone injections than testosterone gel.
- Gels and patches revealed similar risks.
- Testosterone may affect lipid levels when evaluating long-term effects. Therefore, the long-term cardiovascular risks needs to be evaluated.

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